Specification

Retinoid receptor agonist.

The Field of Technology

This invention relates to retinoid receptor active substance having the same physiological action as retinoid such as retinoic acid or the like, or an action to regulate the action of retinoid, and a drug including as an active ingredient the said compound.

Background Technique

Retinoic acid (vitamin A acid) is an active metabolite of vitamin A, and has extremely important physiological effects such as action to cause differentiation of premature developing cells into mature cells having specific function, cell proliferation facilitation action, life maintenance action or the like. Vitamin A derivatives that have been synthesised so far, for example benzoic acid derivative in accordance with Kokai 61-22047 and Kokai 61-76440, compound in accordance with Journal of Medicinal Chemistry (988, Vol. 31, No. 11, p.2182) have been elucidated to have similar physiological effects. The aforesaid compounds having physiological activity of retinoic acid and retinoic acid-like action are known generally as "retinoid".

For example, all-trans retinoic acid binds as ligand to retinoic acid receptor (RAR) belonging to nuclear receptor superfamily (Evans, RM, Science, 240, p.889, 1988) present in cell nucleus, and is known to control the proliferation and differentiation of animal cells or cell death (Petkovich, M, et al., Nature, 330, pp.444-450, 1987). The aforesaid compound having retinoic acid-like physiological activity (for example, 4-[[5,6,7,8-tetrahvdro-5,5,8,8-tetramethvl-2-naphthalenyl] carbamoyl] benzoic acid: Am80 or the like) is suggested to bind to RAR in the same way as retinoic acid, too, and to display physiological activity (cf. Hashimoto, Y, Cell struct. Funct., 16, pp.113-123, 1991, Hashimoto, Y., et al., Biochem-Biophys. Res. Commun., 166, pp.1300-1307, 1990).

These compounds have been found to be clinically useful in prevention and treatment of vitamin A deficiency, keratosis of epithelial tissue, rheumatism, delayed type allergy, bone disease and leukemia and certain types of cancer. However, because these retinoids have various physiological activities, they cannot necessarily be regarded as satisfactory drugs from the viewpoint of side effects. Accordingly, creation of retinoid having characteristic action and the control molecule thereof are desired earnestly.

As action modifier of retinoid, benzodiazepine derivatives such as 4-[5H-2,3-(2,5-dimethyl-2,5-hexano)-5-methyldibenzo[b,e][1,4]diazepin-11-yl] benzoic acid and 4-[1,3-dihydro-7,8-(2,5-dimethyl-2,5-hexano)-2-oxo-2H-1,4-benzodiazepin-5-yl]-benzoic acid or the like are known (PCT/JP96/2709, international disclosure WO97/11061). These compounds do not have retinoid

action by itself or the retinoid action thereof is weak, nevertheless has an action to markedly reinforce the action of retinoid such as retinoic acid or the like, and are suggested to be useful in prevention and treatment of vitamin A deficiency, keratosis of an epithelial tissue, rheumatism, delayed allergy, bone disease or leukemia and certain types of cancer.

As for the expression of physiological activity of retinoic acid, the presence of retinoid X receptor (RXR, 9-cis-retinoic acid is the ligand) is shown. It has been elucidated that the retinoid X receptor forms a dimer with retinoic acid receptor (RAR), and controls expression of physiological activity of retinoic acid by inducing or inhibiting transcription of gene (Mangelsdorf, D.J. et al., Nature, 345, pp.224-229). It has also been elucidated that in addition to retinoic acid receptor (RAR), retinoid X receptor (RXR) binds to receptor of active vitamin D3 in the nucleus, and PPAR said to be involved in fat metabolism, and other receptor species and controls the expression of action of physiologically active substance such as vitamin D3 and thyroxine or the like that bind to these receptors (Mangelsdorf, D. J. et al., the Retinoids, 2nd Ed., Ravan Press, pp.319-350, 1994).

Moreover as retinoid action modifier, presence of the compounds that act antagonistically with respect to retinoid and causes attenuation of typical retinoid actions are also known (Eyrolles, L, et al., Journal of Medicinal Chemistry, 37(10), pp.1508-1517, 1994). For example, it is disclosed in this publication that compounds such as 4-(5H-7,8,9,10-tetrahydro-5,7,7,10,10-pentamethyl benzo[e]naphtho[2,3-b][1,4]diazepin-13-yl) benzoic acid or the like act as antagonist of retinoid. Moreover, compounds such as 4-(13H-10,11,12,13-tetrahydro-10,10,13,13,15-pentamethyl dinaphtho[2,3-b][1,2-e][1,4]diazepin-7-yl) benzoic acid or the like have been found as retinoid antagonist by these inventors (JPA-7-255912 specification).

On the other hand, in the prior art, the carboxyl group of retinoids such as retinoic acid and Am80 or the like or the carboxyl group of the aforesaid retinoid action potentiating compound and retinoid antagonist is considered to be an essential functional group in each desired physiological activity, and when it is substituted with functional group such as sulfonamide, tetrazole or the like, it is known to lose the desired physiological activity. Although compounds having thiazolidine skeleton such as diglitazone, troglitazone or the like are indicated to act on γ subtype of PPAR (peroxisome proliferator-activated receptor) belonging to nuclear receptor superfamily, but in the prior art, it is not at all known that the compounds in which the carboxyl group of the said physiologically active compound was replaced with thiazolidine ring interact with retinoid receptor and display physiological activity.

As thiazolidinedione derivative, N-benzyl type 2,4-thiazolidinedione derivative having blood sugar lowering action is known (Kokai 9-48771 and The 17th medicinal chemistry symposium, The 6th Drug Chemistry sectional meeting annual meeting proceeding collection, pp.114-115, 1-P-30,

October 27, 1997, Pharmaceutical Society of Japan Publication). However, there is no suggestion at all about these thiazolidinedione derivatives have retinoid-like action or function as retinoid action modifier.

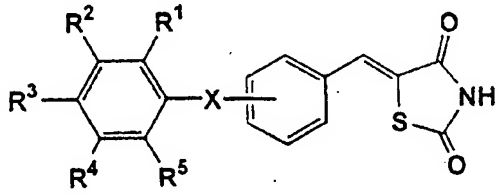
Disclosure of the Invention

The object of this invention is to put forward retinoid receptor active substance having retinoid-like action or control action (for example, action to reinforce or inhibit the action of retinoid) with respect to action of retinoid. Another objection of this invention is to put forward a drug including as an active ingredient the aforesaid compound.

These inventors carried out assiduous investigations, and as a result, discovered that thiazolidine compounds represented by the following general formula had retinoic acid-like biological action, or had action to potentiate or inhibit the action of retinoid. This invention was completed on the basis of this discovery.

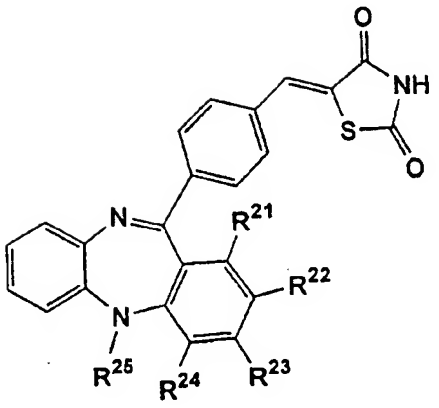
In other words, this invention puts forward:

A compound represented by the following general formula (I)



(wherein, R1, R2, R3, R4 and R5 each independently denote hydrogen atom or lower alkyl group, and among these, two adjacent groups may be linked together with carbon atoms on phenyl ring that they are bonded to form a 5-membered ring or 6-membered ring optionally having alkyl group of more than 1 or 2, X denotes a group represented by -C(R6)=CH-, -CH=C(R7)-, -N(R8)-CO-, -CO-N(R9)-, -C(CHR10), -CO- or -NR11- (wherein, R6, R7, R8, R9, R10 and R11 each independently denote hydrogen atom or lower alkyl group)), or

A compound represented by following general formula (II)



(wherein, R21, R22, R23 and R24 each independently denote hydrogen atom or lower alkyl group, and among these, two adjacent groups may be linked together with carbon atoms on phenyl ring that they are bonded to form a 5-membered ring or 6-membered ring optionally having alkyl group of more than 1 or 2, and R25 denotes a hydrogen atom or lower alkyl group).

From another viewpoint, a drug including as an active ingredient a compound represented by the aforesaid general formula, physiologically acceptable salts thereof and hydrates thereof and the solvate thereof is put forward. This drug is useful as retinoid-like agonist or retinoid action modifier (preferably retinoid action promoter or retinoid action depressant).

From another viewpoint, it is put forward the use of the aforesaid substances for the production of the said drug, and a process of a kind which is a preventive and/or therapeutic process of diseases involving nuclear receptor superfamily (Evans, R.M, Science, 240, p.889, 1988), preferably retinoid receptor (RAR and/or RXR), including a step to administer an effective quantity of the aforesaid substance to mammals including humans.

Ideal form for Carrying Out the Invention

In the aforesaid general formula (I), R1, R2, R3, R4 and R5 each independently denote hydrogen atom or lower alkyl group. As lower alkyl group, it is possible to use carbon number 1-6 approx and preferably carbon number 1-4 straight chain or branched chain alkyl group. For example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group or tert-butyl group or the like can be used.

Moreover, two adjacent groups selected from R1, R2, R3, R4 and R5 may be linked together with carbon atoms on phenyl ring that they are bonded to form one or two, preferably one 5-membered ring or 6-membered ring optionally having alkyl group of more than 1 or 2. As the alkyl group which can be substituted on ring, it is possible to use carbon number 1-6 approx and preferably carbon number 1-4 straight chain or branched chain alkyl group. For example, methyl group, ethyl

group or the like can be used, and it is preferably substituted with 2-4 methyl groups, more preferably 4 methyl groups. For example, 5,6,7,8-tetrahydronaphthalene ring and 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene ring or the like may preferably be formed by R2 and R3 with phenyl ring that R2 and R3 substitute.

X denotes an any group represented by -C(R6)=CH-, -CH=C(R7)-, -N(R8)-CO-, -CO-N(R9)-, -C (CHR10), -CO- or -NR11-. In these groups, R6, R7, R8, R9, R10 and R11 each independently denote hydrogen atom or lower alkyl group, and as lower alkyl group, it is possible to use straight chain or branched chain alkyl group of carbon number 1-4. In a further embodiment, preferably methyl group, ethyl group or the like is used. The site of substitution of X is not restricted in particular on phenyl group of benzylidene thiazolidinedione moiety, however, it is preferably meta-substituted or para-substituted.

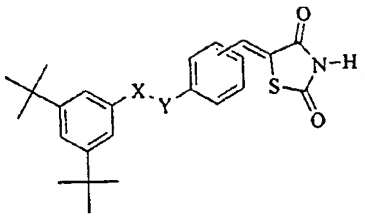
In the aforesaid general formula (II), R21, R22, R23 and R24 each independently denote hydrogen atom or lower alkyl group. As lower alkyl group, it is possible to use carbon number 1-6 approx and preferably carbon number 1-4 of straight chain or branched chain alkyl group. For example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group or tert-butyl group or the like can be used. R25 denotes a hydrogen atom or lower alkyl group, but as lower alkyl group, it is possible to use straight chain or branched chain alkyl group of carbon number 1-4. In a further embodiment, preferably methyl group, ethyl group or the like can be used.

Moreover, two adjacent groups selected from R21, R22, R23 and R24 may be linked together with carbon atoms on phenyl ring that they are bonded to form one or two, preferably one 5-membered ring or 6-membered ring optionally having alkyl group of more than 1 or 2. As the alkyl group which can be substituted on ring, it is possible to use carbon number 1-6 approx and preferably carbon number 1-4 straight chain or branched chain alkyl group. For example, methyl group, ethyl group or the like can be used, and it is preferably substituted with 2-4 methyl groups, more preferably 4 methyl groups. For example, by R22 and R23 with phenyl ring that R22 and R23 substitute, it is preferred 5,6,7,8-tetrahydronaphthalene ring and 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene ring or the like to be formed.

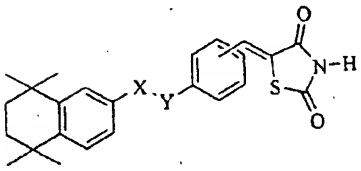
As for the aforesaid compound, base addition salt may be formed, and such salt may present as for example metal salt such as sodium salt, potassium salt, magnesium salt, calcium salt or the like, ammonium salt or organic amine salt or the like such as ethanolamine salt, triethylamine salt or the like. However, the physiologically acceptable salts among such salts can be used as effective ingredient of drug of this invention. Moreover, as for the aforesaid compound, there may be contained 1 or 2 or more asymmetric carbons corresponding to the kind of substituents, and in such case, arbitrary optical isomers on the basis of these asymmetric carbons, arbitrary mixture of optical

isomers, racemic body, diastereoisomer on the basis of asymmetric carbons of two or more, arbitrary mixture of diastereoisomers or the like can be included. Moreover, geometric isomer on the basis of cis- or trans-bond of double bond and arbitrary mixture of geometric isomer, and arbitrary hydrate or solvate of free compound or compound of a salt form, can also be included.

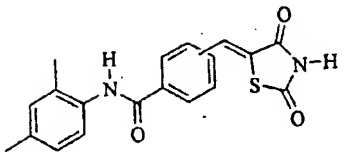
Among the compounds of this invention, the following compounds are nominated as preferred compounds, however, the compounds of this invention or the compounds which can be used as effective ingredient of drug of this invention needs not to be restricted to following compound (in the following explanation, para and meta respectively denotes that the site of substitution of X is para position and meta position on phenyl group of benzylidene thiazolidinedione moiety, and Me denotes methyl group).



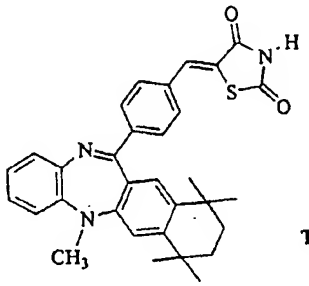
	X	Y	thiazolidine
TZ151	C=O	NH	para
TZ153	C=O	NH	meta
TZ155	NH	C=O	para
TZ157	NH	C=O	meta
TZ161	C=O	NMe	para
TZ163	C=O	NMe	meta
TZ165	NMe	C=O	para
TZ167	NMe	C=O	meta



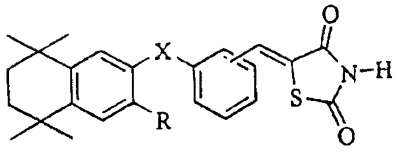
	X	Y	thiazolidine
TZ181	C=O	NH	para
TZ183	C=O	NH	meta
TZ185	NH	C=O	para
TZ187	NH	C=O	meta
TZ191	C=O	NMe	para
TZ193	C=O	NMe	meta
TZ195	NMe	C=O	para
TZ197	NMe	C=O	meta



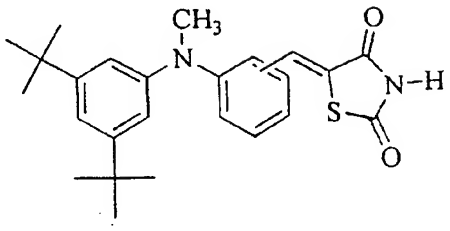
	thiazolidine
TZ175	para
TZ177	meta



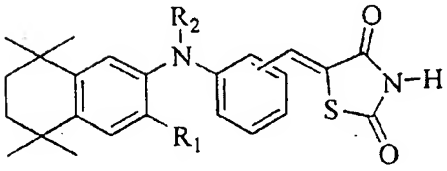
TZ201



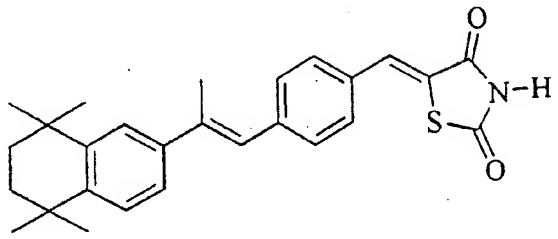
	X	R	thiazolidine
TZ221	C=O	H	para
TZ223	C=O	H	meta
TZ225	C=O	Me	para
TZ227	C=O	Me	meta
TZ241	C=C	H	para
TZ243	C=C	H	meta
TZ245	C=C	Me	para
TZ247	C=C	Me	meta



	thiazolidine
TZ315	para
TZ317	meta



	R_1	R_2	thiazolidine
TZ321	H	H	para
TZ323	H	H	meta
TZ325	H	Me	para
TZ327	H	Me	meta
TZ331	Me	H	para
TZ333	Me	H	meta
TZ335	Me	Me	para
TZ337	Me	Me	meta



TZ91

As for the process for the production of compounds of aforesaid formula (I) and formula (II), Synthesis Examples of the aforesaid representative compounds are described in details in the Examples of this specification. Accordingly, arbitrary compounds included by the compounds of this invention represented by aforesaid general formula (I) or (II) can be easily produced by a person skilled in the art by referring to these Examples or in accordance with requirements by adding suitable alteration or modification to these processes.

Compound of the aforesaid formula (I) and formula (II) can interact with respect to retinoid receptor (the term of "retinoid receptor" used in this specification includes retinoic acid receptor RAR and RXR, and refers to one or two or more receptors with which retinoids such as retinoic

acid or the like can interact), and it either displays retinoid-like physiological activity by itself as agonist or has an action to enhance or inhibit the physiological activity of retinoid.

Accordingly, the drug including as an active ingredient the aforesaid compound is useful as retinoid-like agonist or retinoid action modifier. Which of the aforesaid action is displayed by the compound of the aforesaid formula (I) and formula (II) can be easily confirmed by the process described in detail in Examples of this specification. Moreover, there is a description in international disclosure WO97/11061 (PCT/JP96/2709) about evaluation process of retinoid action potentiating compound, and there is description in Eyrolles, L., et al., Journal of Medicinal Chemistry, 37(10), pp.1508-1517, 1994 and JPA-7-255912 specification about the evaluation process of retinoid action inhibitory compound.

Among the aforesaid compounds, the compounds having retinoid-like action have for example cell differentiation action, cell proliferation facilitation action, and life maintenance action or the like, and it can be used as effective ingredient of drug for prevention / therapy of vitamin A deficiency, keratosis of an epithelial tissue, psoriasis, allergic disease, immunologic disease such as rheumatism or the like, bone disease, leukemia or cancer.

Moreover, among the aforesaid compounds, the retinoid action potentiating compounds do not substantially have retinoid-like action, or have weak to moderate retinoid-like action, nevertheless, when the said compounds are placed in the co-presence of retinoid such as retinoic acid or the like, the physiological activity of retinoid (as typical examples, cell differentiation action, cell proliferation facilitation action, and life maintenance action or the like) is markedly enhanced.

No specific theory is adhered to, but when such retinoid action potentiating compound itself contains retinoid-like action, then the action thereof is synergistic action. Accordingly, when retinoids including retinoic acid or the aforesaid compound having retinoic acid-like biological action (for example, 4-[[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl] carbamoyl] benzoic acid: Am80) is administered as a drug for prevention or therapy of vitamin A deficiency, keratosis of epithelial tissue, psoriasis, allergic disease, immunologic disease such as rheumatism or the like, bone disease, leukemia or cancer, retinoid action potentiating compound can be used as action promoter of said retinoid.

Moreover, the aforesaid retinoid action potentiating compound enhances the action of retinoic acid present in the body even when retinoid is not administered for prevention or therapy of the said diseases, therefore, the aforesaid compound can be administered as a drug for the purpose of prevention or therapy of the said diseases. Furthermore, not only can these compounds have action potentiation with respect to retinoid, but also be used as action enhancer of physiologically active

substances such as steroidal compound, vitamin D compound such as vitamin D3 or the like or thyroxine or the like, which display physiological effect by binding to receptors belonging to nuclear receptor superfamily (Evans, RM, Science, 240, p.889, 1988) which is present in the nucleus of the cell. For example, it is useful as drug for prevention and/or therapy of diseases such as diabetes mellitus, arteriosclerosis, hyperlipidemia, hypercholesterolemia, bone disease, rheumatism or immunologic disease or the like.

As such nuclear receptors, for example, nuclear receptor of active vitamin D3, PPAR participating in fat metabolism, thyroxine receptor, and COUP or the like are known (as for the aforesaid receptors, cf. Mangelsdorf, D.J. et al., the Retinoids, 2nd Ed., Ravan Press, pp.319-350, 1994), it has been elucidated that these receptors in each case display the action of the said physiologically active substances by binding to retinoid X receptor (RXR).

Among the aforesaid compounds, retinoid action inhibitory compounds have action to markedly inhibit physiological action of retinoid (as typical examples, cell differentiation action, cell proliferation facilitation action, and life maintenance action or the like). No specific theory is adhered to, but it is considered that the compounds having such action bind to retinoid X receptor (RXR) that forms a dimer with retinoic acid receptor (RAR), and control the expression of physiological activity of retinoid such as retinoic acid or the like. These compounds are useful for prevention and/or therapy of endogenous vitamin A excess due to excess vitamin A in body, or exogenous vitamin A excess induced by retinoic acid or compound having retinoic acid-like biological action (for example, 4-[[5,6,7,8-tetrahvdro-5,5,8,8-tetramethyl-2-naphthalenyl] carbamoyl] benzoic acid: Am80) to be administered for prevention or therapy of vitamin A deficiency, keratosis of epithelial tissue, psoriasis, allergic disease, immunologic disease such as rheumatism or the like, bone disease, leukemia or cancer.

The retinoid action inhibitory compound can be administered by itself or in combination with other retinoid and anti-cancer agent, thereby cancer such as leukemia or the like can be treated. Moreover, the aforesaid compounds can suppress the action of substances, which display physiological effect by binding to receptors belonging to nuclear receptor superfamily (Evans, RM, Science, 240, p.889, 1988) which is present in the nucleus of the cell, such as steroidal compound, vitamin D compound such as vitamin D3 or the like or thyroxine or orphan receptor with unknown ligand or the like, therefore can be used for controlling the expression of the physiological action of these substances. Accordingly, the retinoid action inhibitory compound that binds to retinoid X receptor (RXR) can be used for prevention and/or therapy of diseases accompanied by aberration of biological action involving 1 or 2 or more of nuclear receptors belonging to nuclear receptor superfamily.

Drug of this invention contains as an active ingredient at least one of substance selected from the group comprising compound represented by the aforesaid formula (I), salts thereof, and hydrates thereof and solvate, or substance selected from the group comprising compound represented by the aforesaid formula (II), salts thereof and hydrates thereof and solvate. As drug of this invention, the aforesaid substance may be administered by itself, but preferably, it can be administered as medicinal composition of oral use or parenteral use that can be produced by process well-known to a person skilled in the art. As composition for drug suited for oral administration, for example, tablet, encapsulated formulation, powder, fine granules, granule, liquid agent and syrup or the like may be proposed, and for example injection, suppository, inhalant, instillation, collunarium, ointment, cream agent, and patch or the like are nominated as the medicinal composition suitable for parenteral administration.

The aforesaid medicinal composition can be produced by addition of pharmacologically and pharmaceutically permitted additives. For example, as examples of pharmacologically and pharmaceutically permitted additives, excipient, disintegrating agent or disintegration adjuvant, binding agent, lubricant, coating agent, dye, diluent, base, solvent or solubilizer, isotonizing agent, pH modifier, stabilising agent, propellant, and binder or the like may be proposed.

Dose of drug of this invention is not restricted in particular, and it can be suitably selected corresponding to kind of action thereof or the strength and weakness or the like for a product, and also it is possible to suitably increase and decrease corresponding to various kinds of factors to be considered such as body weight, age of the patient, type of diseases, symptoms, administration route or the like. Generally, for the drug containing as an active ingredient compound having retinoid-like action, the dose thereof is referred to in accordance with the dose used for retinoic acid or the like as drug, and it can be suitably selected. For example, in case of oral administration, it is possible to be used with range of about 0.01-1,000mg per day per adult. Moreover, the dose can be selected in the same way about the drug including as an active ingredient retinoid action potentiating or retinoid action inhibitory compound, and it can be used per day per adult with range of about 0.01-1,000mg in the case of oral administration.

Examples

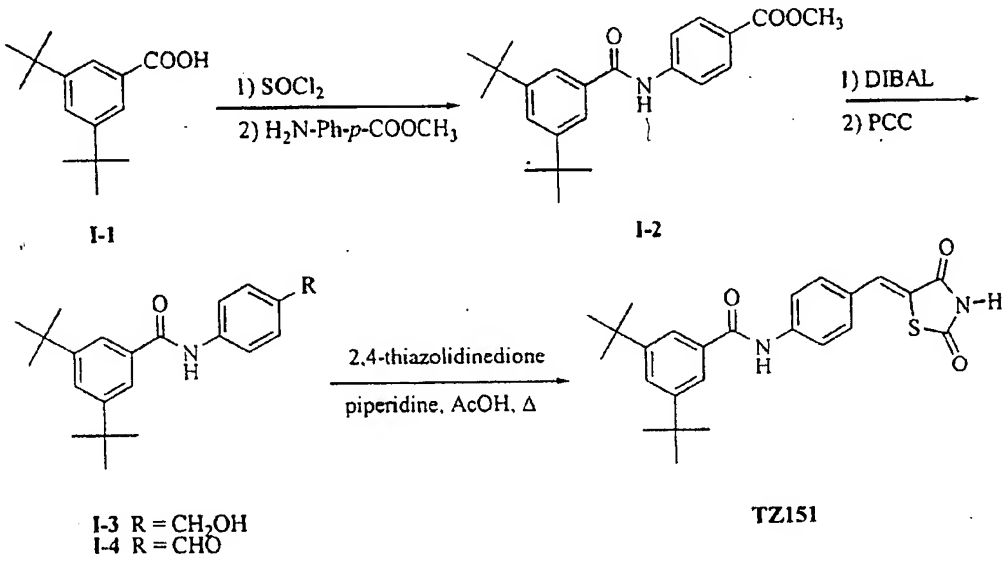
Hereinafter, this invention will be described in greater detail using Examples. However, the range of the invention needs not to be restricted to the range of the following Examples. Moreover, the compound number in Examples corresponds to the number shown as preferred examples as above and the following synthesis scheme.

Example 1: Synthesis of TZ91.

4-[2-(5,6,7,8-tetramethyl-5,5,8,8-tetrahydro-2-naphthyl) propenyl] benzaldehyde 24 mg (0.072 mmol), 2,4-thiazolidinedione 10 mg (0.085 mmol) and piperidine 5 mg (0.058 mmol) were dissolved in ethanol 2.5 ml, and it was refluxed overnight. The reaction liquid was poured into 1N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was washed with water, and it was dewatered with Na_2SO_4, and after the elimination of the solvent, it was recrystallised from methanol, and TZ91 (quantitative) was obtained.

TZ91: Yellow needles (methanol), mp 227-229°C; ^{1}H-NMR (400MHz, $CDCl_3$) 8.24 (br s, 1H), 7.87 (s, 1H), 7.51 (d, 2H, J = 8.8 Hz), 7.48 (d, 2H, J = 8.8 Hz), 7.45 (d, 1H, J = 1.5 Hz), 7.33 (d, 1H, J = 8.4 Hz), 7.30 (dd, 1H, J = 8.4, 1.8 Hz), 6.78 (br s, 1H), 2.32 (d, 3H, J = 1.5 Hz), 1.71 (s, 4H), 1.34 (s, 6H), 1.31 (s, 6H),
Anal. Calcd. for C27H29NO2S, C= 75.15%, H= 6.77%, N, 3.25%,
Found C= 75.08%, H = 6.97 %, N, 3.11%.

Example 2: Synthesis of TZ151.



I-3 R = CH_2OH
I-4 R = CHO

3,5-di-tert-butyl benzoic acid (I-1) 1.00 g (4.27 mmol) was suspended in thionyl chloride 2.50 g (21.0 mmol), anhydrous benzene 12 ml, and the suspension was refluxed for 14 hours. The thionyl chloride was eliminated by distillation, and p-aminobenzoic acid methyl ester 645mg (4.27 mmol) was added, and it was suspended in anhydrous benzene 30 ml, anhydrous pyridine 1 ml, and the mixture was stirred at room temperature for one hour 30 minutes. Iced water, 2N hydrochloric acid were added to the reaction liquid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and it was

concentrated. It was purified by silica gel column chromatography (methylene chloride) and Compound I-2 was obtained 1.03 g (66 %).
^{1}H-NMR (400 MHz, $CDCl_3$) 8.06 (d, 2H, J= 8.8 Hz), 7.90 (br s, 1H), 7.75 (d, 2H, J = 8.8 Hz), 7.66 (d, 2H, J = 1.5 Hz), 7.64 (t, 1H, J = 1.8 Hz), 3.92 (s, 3H), 1.37 (s, 18H).

Compound 1-2, 1.02 g (2.78 mmol) was dissolved in THF 30 mL, and DIBAL 8.34 mL (1M toluene solution, 8.34 mmol) was gradually added at –20°C. 30 minutes later, the reaction liquid was discharged into 2N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 1) and Compound I-3 was obtained 786 mg (83 %).
^{1}H-NMR (400MHz, $CDCl_3$) 7.78 (br s, 1H), 7.67 (d, 2H, J = 1.8 Hz), 7.65 (d, 2H, J = 8.8 Hz), 7.62 (t, 1H, J = 1.8 Hz), 7.38 (d, 2H, J = 8.8 Hz), 4.69 (d, 2H, J = 5.9 Hz), 1.37 (s, 18H).

Compound I-3, 780 mg (2.30 mmol) was dissolved in methanol-free methylene chloride 22 ml, and PCC 992mg (4.60 mmol) was added and the mixture was stirred at room temperature for two hours 30 minutes. The reaction liquid was concentrated, and it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and Compound I-4 was obtained 704 mg (91 %).
^{1}H-NMR (400MHz, $CDCl_3$) 9.96 (s, 1H), 7.97 (brs, 1H), 7.92 (d, 2H, J = 8.4 Hz), 7.85 (d, 2H, J = 8.4 Hz), 7.67 (d, 2H, J = 1.8 Hz), 7.66 (t, 1H, J = 1.8 Hz), 1.38 (s, 18H).

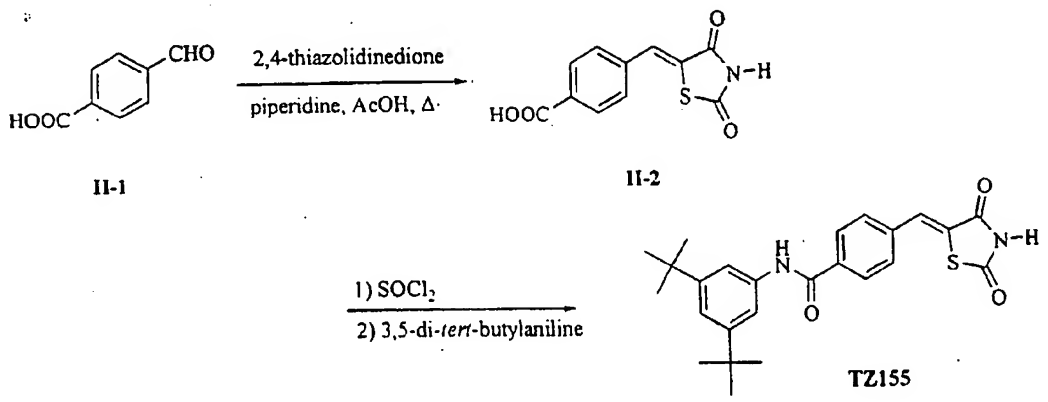
Compound I-4, 150mg (0.45 mmol), 2,4-thiazolidinedione 52 mg (0.45 mmol) were suspended in anhydrous toluene 10 ml, and a solution comprising piperidine 11 mg (0.13 mmol) and acetic acid 8 mg (0.13 mmol) dissolved in anhydrous toluene 1.4 ml was added, and the mixture was refluxed at 120°C for three hours 30 minutes. The reaction liquid was discharged into iced water and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and it was dewatered at $MgSO_4$, and thereafter the solvent was concentrated, and TZ151 was obtained 194 mg (99 %).

TZ151: Yellow powder (ethyl acetate / n-hexane); mp >300°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 10.43 (s, 1H), 7.93 (d, 2H, J = 8.4 Hz), 7.75 (s, 1H), 7.74 (d, 2H, J = 1.8 Hz), 7.63 (m, 3H), 1.35 (s, 18H),
Anal. Calcd. for C25H28N2O3S, C= 68.78%, H= 6.46%, N= 6.42%,
Found C= 68.70%, H= 6.59%, N = 6.15 %.

Example 3: Synthesis of TZ153.
3,5-di-tert-butyl benzoic acid (I-1) and m-aminobenzoic acid methyl ester were used as the starting materials, and TZ153 was synthesised according to the process of Example 2.

TZ153: Pale yellow powder (ethyl acetate / n-hexane); mp 252°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 10.36 (s, 1H), 8.16 (brs, 1H), 7.76 (m, 4H), 7.63 (t, 1H, J = 1.8 Hz), 7.52 (t, 1H, J = 8.1 Hz), 7.37 (d, 1H, J = 8.0 Hz), 1.35 (s, 18H);
Anal. Calcd. for C25H28N2O3S, C= 68.78%, H= 6.46%, N= 6.42%,
Found C= 68.81%, H= 6.60%, N = 6.59 %.

Example 4: Synthesis of TZ155.

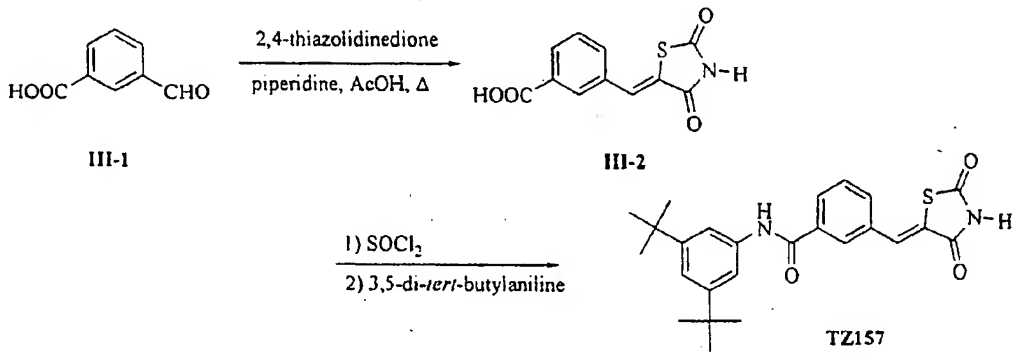


p-formyl benzoic acid (II-1) 1.00 g (6.67 mmol), 2,4-thiazolidinedione 858 mg (7.33 mmol) were suspended in anhydrous toluene 40 ml. The solution of piperidine 170 mg (2.00 mmol), acetic acid 120 mg (2.00 mmol) dissolved in anhydrous toluene 20 ml was added, and the mixture was refluxed at 120°C for six hours. The reaction liquid was cooled to room temperature, and the precipitated crystals were recovered by filtration and were washed with toluene, benzene, and 20 % acetone aqueous solution, and then dried, and Compound II-2 was obtained 1.57 g (94 %).
^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 8.04 (d, 2H, J = 8.4 Hz), 7.79 (s, 1H), 7.70 (d, 2H, J = 8.4 Hz).

Compound II-2, 250mg (1.00 mmol) was suspended in anhydrous benzene 12 ml, and $SOCl_2$ 627mg (5.27 mmol) was added, and the mixture was refluxed for 14 hours. $SOCl_2$ was eliminated by distillation, and thereafter, it was suspended in anhydrous benzene 10 ml, and 3,5-di-tert-butyl aniline 210 mg (1.00 mmol), anhydrous pyridine 4 ml were added, and the mixture was stirred at room temperature for two hours. 2N hydrochloric acid with floating ice was added to the reaction liquid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 3 : 2) and TZ155 was obtained 390 mg (89 %).

TZ155: Pale yellow powder (ethyl acetate / n-hexane); mp 266-267°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 10.20 (s, 1H), 8.08 (d, 2H, J = 8.4 Hz), 7.87 (s, 1H), 7.74 (d, 2H, J = 8.4 Hz), 7.69 (d, 1H, J = 1.5 Hz), 7.16 (t, 1H, J = 1.5 Hz), 1.30 (s, 18H),
Anal. Calcd. for C25H28N2O3S, C= 68.78%, H= 6.46%, N= 6.42%,
Found C= 68.52%, H= 6.52%, N = 6.37%.

Example 5: Synthesis of TZ157.



m-formyl benzoic acid (III-1) 800 mg (5.33 mmol), 2,4-thiazolidinedione 686 mg (5.87 mmol) were suspended in anhydrous toluene 40 ml. Solution comprising piperidine 136 mg (1.60 mmol), acetic acid 96 mg (1.60 mmol) dissolved in anhydrous toluene 16 ml was added, and the mixture was refluxed at 120°C for four hours 30 minutes. The reaction liquid was cooled to room temperature, and the precipitated crystals were recovered by filtration and were washed with toluene, benzene, and 20 % acetone aqueous solution. and then dried, and Compound III-2 was obtained 1.017 g (77 %).
^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 8.14 (s, 1H), 8.01 (d, 1H, J = 7.7 Hz), 7.86 (s, 1H), 7.85 (d, 1H, J = 7.7 Hz), 7.66 (t, 1H, J = 7.7 Hz).

Compound III-2, 250mg (1.00 mmol) was suspended in anhydrous benzene 14 ml, and $SOCl_2$ 627mg (5.27 mmol) was added, and the mixture was refluxed for 14 hours. $SOCl_2$ was eliminated by distillation, and thereafter, it was suspended in anhydrous benzene 10 ml, and 3,5-di-tert-butyl aniline 210 mg (1.00 mmol), anhydrous pyridine 4 ml were added, and the mixture was stirred at room temperature for two hours. 2N hydrochloric acid that ice was floated on was added to the reaction liquid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 3 : 4) and TZ157 was obtained 292 mg (67 %).

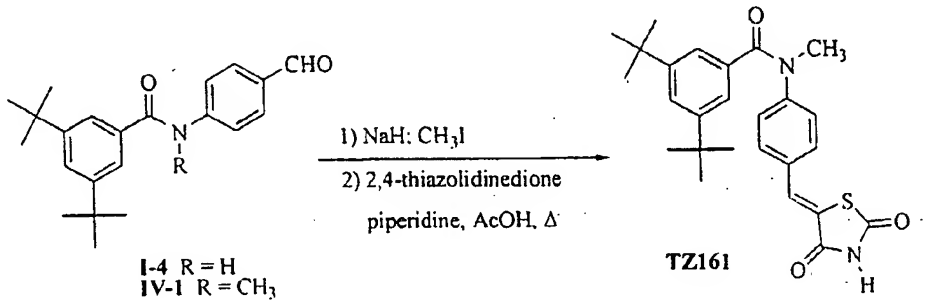
TZ157: Colorless needles (ethyl acetate / n-hexane); mp 263°C

^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 10.20 (s, 1H), 8.15 (s, 1H), 8.04 (d, 1H, J = 7.7 Hz), 7.87 (s, 1H), 7.78 (d, 1H, J = 7.7 Hz), 7.69 (t, 1H, J = 7.7 Hz), 7.67 (d, 2H, J = 1.5 Hz), 7.17 (t, 1H, J = 1.5 Hz), 1.30 (s, 18H),

Anal. Calcd. for C25H23N2O3S, C= 68.78%, H= 6.46%, N= 6.42%,

Found C= 68.82%, H= 6.65%, N = 6.56 %.

Example 6: Synthesis of TZ161.



I-4 R = H
IV-1 R = CH_3

TZ161

NaH 97.6mg (60 %, 2.45 mmol) was washed with n-hexane, and it was suspended in DMF 1 ml. Aldehyde I-4 (cf. Example 2) 550 mg (1.63 mmol) dissolved in DMF 10 ml was added, and the mixture was stirred at room temperature for 20 minutes. Methyl iodide 0.19 ml (3.05 mmol) was added, and the mixture was stirred for 45 minutes. The DMF was eliminated by distillation, water was added and the mixture was extracted with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and Compound IV-1 was obtained 389 mg (68 %).

^{1}H-NMR (400MHz, $CDCl_3$) 9.90 (s, 1H), 7.73 (d, 2H, J = 8.4 Hz), 7.31 (t, 1H, J = 1.8 Hz), 7.31 (t, 1H, J = 1.8 Hz), 7.15 (d, 2H, J = 8.4 Hz), 7.13 (d, 2H, J = 1.8 Hz), 3.56 (s, 3H), 1.14 (s, 18H).

Compound IV-1, 385mg (1.10 mmol), 2,4-thiazolidinedione 128 mg (1.10 mmol) were suspended in anhydrous toluene 8 ml, and a solution of piperidine 26 mg (0.33 mmol) and acetic acid 20 mg (0.33 mmol) dissolved in anhydrous toluene 3 ml was added, and the mixture was refluxed at 120°C for one hour 30 minutes. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 1) and TZ161 was obtained 417 mg (84.5 %).

TZ161: Yellow plate (ethyl acetate / n-hexane); mp 265°C
^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 7.70 (s, 1H), 7.46 (d, 2H, J = 8.4 Hz), 7.29 (t, 1H, J = 1.5 Hz), 7.26 (d, 2H, J = 8.4 Hz), 7.09 (d, 2H, J = 1.5 Hz), 3.41 (s, 3H), 1.12 (s, 18H),
Anal. Calcd. for C26H30N2O3S, C= 69.31%, H= 6.71%, N= 6.22%,
Found C= 69.01%, H= 6.68%, N = 5.93 %.

Example 7: Synthesis of TZ163.
3-(3,5-di-tert-butylphenyl carbamoyl) benzaldehyde (synthesised in the same way as in Compound 1-4 from m-amino benzoic acid methyl ester) was used as starting material. TZ163 was synthesised according to the process of Example 6.

TZ163: Yellow plates (ethyl acetate / n-hexane); mp 195°C, ^{1}H-NMR1R (400 MHz, DMSO-d_6, 30°C) 7.61 (s, 1H), 7.46 (t, 1H, J = 7.7 Hz), 7.38 (m, 2H), 7.27 (t, 1H, J = 1.8 Hz), 7.14 (brs, 1H), 7.08 (d, 2H, J = 1.8 Hz), 3.42 (s, 3H), 1.11 (s, 18H),
Anal. calcd. For C26H30N2O3S, C= 69.31%, H= 6.71%, N= 6.22%,
Found C= 69.41%, H= 6.92%, N = 5.99 %.

Example 8: Synthesis of TZ165.
Thiazolidine II-2 (cf. Example 4) and 3,5-di-tert-butyl-N-methylaniline were used as starting materials. TZ165 was synthesised according to the process of Example 4 (79 %).

TZ165: Pale yellow prisms (ethyl acetate / n-hexane); mp 253-254°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 7.67 (s, 1H), 7.38 (d, 2H, J = 8.4 Hz), 7.29 (d, 2H, J = 8.4 Hz), 7.11 (s, 1H), 6.93 (s, 2H), 3.42 (s, 3H), 1.12 (s, 18H),
Anal. Calcd. for C26H30N2O3S, C= 69.31%, H= 6.71%, N= 6.22%,
Found C= 69.05%, H= 6.53%, N = 6.48 %.

Example 9: Synthesis of TZ167.
Thiazolidine III-2 (cf. Example 5) and 3,5-di-tert-butyl-N-methylaniline were used as starting materials. TZ167 was synthesised according to the process of Example 5 (76 %).

TZ167: Colorless prisms (ethyl acetate / n-hexane); mp 238°C
^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 7.58 (s, 1H), 7.48 (m, 2H) 7.23 (brs, 1H), 7.10 (s, 1H), 6.93 (d, 2H, J = 1.5 Hz), 3.44 (s, 3H), 1.11 (s, 18H),
Anal. Calcd. for C26H30N2O3S, C= 69.31%, H= 6.71%, N= 6.22%,
Found C= 69.13%, H= 6.78%, N = 6.34 %.

Example 10: Synthesis of TZ175.

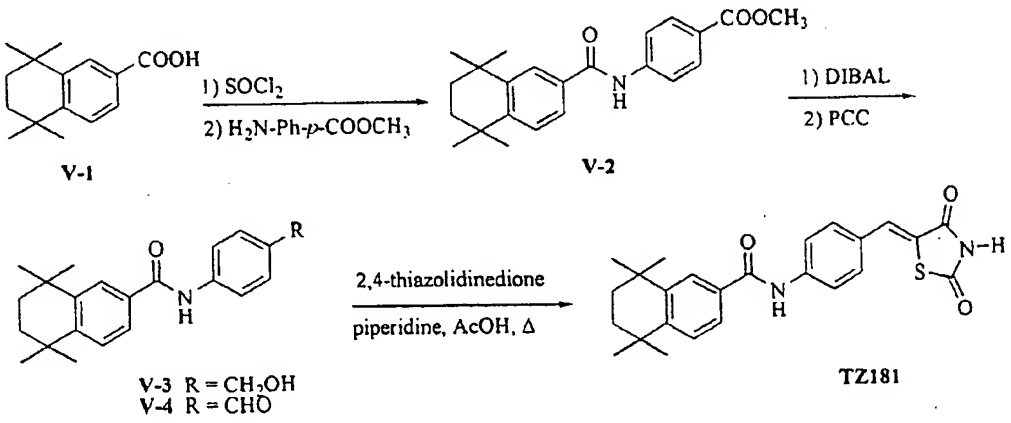
2,4-xylidine and thiazolidine II-2 (cf. Example 4) were used as starting materials. TZ175 was synthesised according to the process of Example 4 (88 %).

TZ175: Pale pink powder (methylene chloride / methanol); mp 269°C
^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 9.89 (s, 1H), 8.08 (d, 2H, J = 8.4 Hz), 7.86 (s, 1H), 7.73 (d, 2H, J = 8.4 Hz), 7.21 (d, 1H, J = 8.1 Hz), 7.08 (s, 1H), 7.02 (d, 1H, J = 8.1 Hz), 2.29 (s, 3H), 2.20 (s, 3H),
Anal. Calcd. for C19H16N2O3S, C= 64.76%, H= 4.58%, N= 7.95%,
Found C= 64.51%, H= 4.67%, N = 8.07 %.

Example 11: Synthesis of TZ177.
2,4-xylidine and thiazolidine III-2 (cf. Example 5) were used as starting materials. TZ177 was synthesised according to the process of Example 5 (31 %).

TZ177: Colorless needles (methylene chloride / methanol); mp 245°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 9.90 (s, 1H), 8.15 (s, 1H), 8.04 (d, 1H, J = 7.7 Hz), 7.87 (s, 1H), 7.79 (d, 1H, J = 8.1 Hz), 7.68 (t, 1H, J = 7.7 Hz), 7.23 (d, 1H, J = 8.1 Hz), 7.09 (s, 1H), 7.03 (d, 1H, J = 8.1 Hz), 2.29 (s, 3H), 2.21 (s, 3H),
Anal. Calcd. for C19H16N2O3S, C= 64.76%, H= 4.58%, N= 7.95%,
Found C= 64.57%, H= 4.41%, N = 7.89 %.

Example 12: Synthesis of TZ181.



5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoic acid (V-1) 700 mg (3.01 mmol) was suspended in thionyl chloride 8 ml and 1 drop of DMF was added and the mixture was stirred at room temperature for two hours. The thionyl chloride was eliminated by distillation, and p-aminobenzoic

acid methyl ester 450mg (2.98 mmol) and 4-dimethylaminopyridine 5 mg were added, and it was dissolved in anhydrous pyridine 20 ml, and the mixture was stirred at room temperature overnight. The reaction liquid was poured into 2N hydrochloric acid, and extraction was carried out with ethyl acetate. The organic layer was washed with 2N hydrochloric acid, water, and aqueous sodium chloride, and it was dewatered with Na_2SO_4, and it was concentrated, and compound V-2 was obtained (97 %).

Compound V-2, 183mg (0.50 mmol) was dissolved in THF 10 mL, and DIBAL I.5 mL (1M toluene solution, 1.5 mmol) was added at –45°C. 30 minutes later, the reaction liquid was discharged into 2N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with Na_2SO_4, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : methylene chloride = 1 : 3) and compound V-3 was obtained 142 mg (84 %).
^{1}H-NMR (400MHz, $CDCl_3$) 7.86 (d, 1H, J = 2.2 Hz), 7.78 (brs, 1H), 7.63 (d, 2H, J = 8.4 Hz), 7.55 (dd, 1H, J = 2.0, 8.2 Hz), 7.40 (d, 1H, J = 8.8 Hz), 7.37 (d, 2H, J = 8.4 Hz), 4.68 (s, 2H), 1.72 (s, 4H), 1.33 (s, 6H), 1.31 (s, 6H).

Compound V-3, 140mg (0.42 mmol) was dissolved in methanol-free methylene chloride 10 ml, and PCC 100mg (0.46 mmol) was added and the mixture was stirred at room temperature for one hour. The reaction liquid was concentrated, and it was purified by silica gel column chromatography (methylene chloride) and compound V-4 was obtained 99 mg (71 %).
^{1}H-NMR (400MHz, $CDCl_3$) 9.95 (s, 1H), 7.92 (brs, 1H), 7.91 (d, 2H, J = 8.8 Hz), 7.87 (d, 1H, J = 1.8 Hz), 7.84 (d, 2H, J = 8.8 Hz), 7.56 (dd, 1H, J = 2.0, 8.3 Hz), 7.43 (d, 1H, J = 8.4 Hz), 1.73 (s, 4H), 1.34 (s, 6H), 1.32 (s, 6H).

Compound V-4, 73mg (0.22 mmol), 2,4-thiazolidinedione 30 mg (0.26 mmol) were suspended in anhydrous toluene 4 ml. Piperidine 173 µl and acetic acid 100 µl were dissolved in anhydrous toluene 25 ml, and solution 3 ml thereof were added, and it was refluxed at 120°C for two hours. The reaction liquid was discharged into iced water and extraction was carried out with ethyl acetate. The organic layer was washed with 2N hydrochloric acid, water, it was dewatered with Na_2SO_4, thereafter the solvent was concentrated, and TZ181 was obtained 100 mg (quantitative).

TZ181: Yellow needles (ethyl acetate / n-hexane); mp 288-290°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 12.52 (s, 1H), 10.36 (s, 1H), 7.94 (d, 2H, J = 8.8 Hz), 7.88 (d, 1H, J = 2.2 Hz), 7.76 (s, 1H), 7.71 (dd, 2H, J = 2.2, 8.4 Hz), 7.60 (d, 2H, J = 8.8 Hz), 7.48 (d, 1H, J = 98.3 Hz), 1.68 (s, 4H), 1.31 (s, 6H), 1.28 (s, 6H),
Anal. Calcd. for C25H26N2O3S, C= 69.10%, H= 6.03%, N= 6.45%,
Found C= 69.05%, H= 6.23%, N = 6.55 %.

Example 13: Synthesis of TZ183.

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoic acid (V-1) and m-aminobenzoic acid methyl ester were used as starting materials. TZ183 was synthesised according to the process of Example 12.

TZ183: Colorless powder (ethyl acetate / n-hexane); mp 183°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 10.29 (s, 1H), 8.15 (s, 1H), 7.88 (d, 1H, J = 1.8 Hz), 7.76 (d, 1H, J = 1.8 Hz), 7.26 (s, 1H), 7.26 (s, 1H), 6.71 (dd, 1H, J = 8.4Hz, 1.8 Hz), 6.50 (t, 1H, J = 7.7 Hz), 6.49 (d, 1H, J = 8.1 Hz), 6.35 (d, 1H, J = 2.1 Hz), 1.69 (s, 4H), 1.31 (s, 6H), 1.28 (s, 6H),
Anal. Calcd. for C25H26N2O3S, C= 69.10%, H= 6.03%, N= 6.45%,
Found C= 68.81%, H= 5.92%, N = 6.51 %.

Example 14: Synthesis of TZ185.

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine and thiazolidine II-2 (cf. Example 4) were used as starting materials. TZ185 was synthesised according to the process of Example 4.

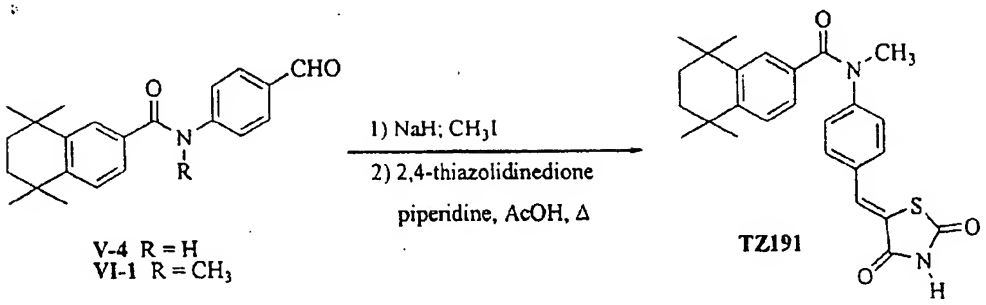
TZ185: Pale orange plates (ethyl acetate / n-hexane); mp 234°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 10.18 (s, 1H), 8.07 (d, 2H, J = 8.4 Hz), 7.86 (s, 1H), 7.73 (d, 2H, J = 8.4 Hz), 7.68 (d, 1H, J = 2.2 Hz), 7.57 (dd, 1H, J = 8.4Hz, 2.2 Hz), 7.28 (d, 1H, J = 8.4 Hz), 1.65 (s, 4H), 1.25 (s, 6H), 1.24 (s, 6H),
Anal. Calcd. for C25H26N2O3S, C= 69.10%, H= 6.03 %, N= 6.45
Found C= 69.40%, H= 6.10%, N= 6.55%.

Example 15: Synthesis of TZ187.

5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine and thiazolidine III-2 (cf. Example 5) were used as starting materials. TZ187 was synthesised according to the process of Example 5.

TZ187: Colorless plates (ethyl acetate / n-hexane); mp 187°C, ^{1}H-NMR (40 MHz, DMSO-d_6, 30°C) 10.18 (s, 1H), 8.14 (s, 1H), 8.03 (d, 2H, J = 7.7 Hz), 7.87 (s, 1H), 7.78 (d, 1H, J = 7.7 Hz), 7.68 (t, 1H, J = 7.7 Hz), 7.68 (d, 1H, J = 2.2 Hz), 7.56 (dd, 1H, J = 8.8Hz, 2.2 Hz), 7.29 (d, 1H, J = 8.4 Hz), 1.65 (s, 4H), 1.26 (s, 6H), 1.24 (s, 6H),
Anal. Calcd. for C25H26N2O3S, C= 69.10%, H= 6.03%, N= 6.45%,
Found C= 68.81%, H= 6.21%, N = 6.37 %.

Example 16: Synthesis of TZ191.



V-4 R = H
VI-1 R = CH_3

TZ191

NaH 18mg (60 %, 0.45 mmol) was washed with n-hexane, and it was suspended in DMF 1 ml. Aldehyde V-4 (cf. Example 12) 100 mg (0.30 mmol) was dissolved in DMF 4 ml, and it was added and the mixture was stirred at room temperature for 15 minutes. Methyl iodide 0.07 ml (1.12 mmol) was added, and the mixture was stirred for 30 minutes. The DMF was eliminated by distillation, water was added and the mixture was extracted with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dehydrated with $MgSO_4$, thereafter, the solvent were concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and compound VI-1 was obtained 388.9 mg (63 %).
^{1}H-NMR (400MHz, $CDCl_3$) 9.92 (s, 1H), 7.75 (d, 2H, J = 8.4 Hz), 7.24 (dd, 1H, J = 8.1, 1.8 Hz), 7.19 (d, 1H, J = 8.4 Hz), 7.18 (d, 1H, J = 8.4 Hz), 7.04 (d, 1H, J = 1.8 Hz), 3.55 (s, 3H), 1.60 (m, 4H), 1.20 (s, 6H), 0.93 (s, 6H).

Compound VI-1, 60 mg (0.17 mmol), 2,4-thiazolidinedione 20 mg (0.17 mmol) were suspended in anhydrous toluene 4 ml, and a solution of piperidine 4.4 mg (0.052 mmol) and acetic acid 3.1 mg (0.052 mmol) dissolved in anhydrous toluene 0.5 ml was added, and the mixture was refluxed at 120°C for 40 minutes. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and TZ191 was obtained 417 mg (93 %).

TZ191: Yellow powder (ethyl acetate / n-hexane); mp 235°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 7.71 (s, 1H), 7.48 (d, 2H, J = 8.8 Hz), 7.28 (d, 2H, J = 8.4 Hz), 7.27 (d, 1H, J = 8.4 Hz), 7.22 (dd, 1H, J = 8.4, 1.5 Hz), 6.98 (d, 1H, J = 1.8 Hz), 3.40 (s, 3H), 1.53 (m, 4H), 1.17 (s, 6H), 0.89 (s, 6H),
Anal. Calcd. for C26H28N2O3S, C= 69.62%, H= 6.29%, N= 6.24%,
Found C= 69.33%, H= 6.38%, N = 6.31%.

Example 17: Synthesis of TZ193.

3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl carbamoyl) benzaldehyde (synthesied in the same way as in compound V-4 from m-aminobenzoic acid methyl ester) was used as starting material. TZ193 was synthesised according to the process of Example 16.

TZ193: Colorless plates (ethyl acetate / n-hexane); mp 188°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 7.64 (s, 1H), 7.47 (t, 1H, J = 7.7 Hz), 7.38 (m, 2H), 7.24 (d, 1H, J = 8.1 Hz), 7.16 (dd, 1H, J = 8.4, 1.8 Hz), 7.03 (d, 1H, J = 1.8 Hz), 3.41 (s, 3H), 1.52 (s, 4H), 1.14 (s, 6H), 0.91 (s, 6H),
Anal. Calcd. for C26H28N2O3S, C= 69.62%, H= 6.29%, N= 6.24%,
Found C= 69.65%, H= 6.16%, N = 6.08 %.

Example 18: Synthesis of TZ195.

It was synthesised (80 %) according to the process of Example 4 from thiazolidine II-2 (cf. Example 4) and 5,6,7,8-tetrahydro-N,5,5,8,8-pentamethyl-2-naphthylamine.

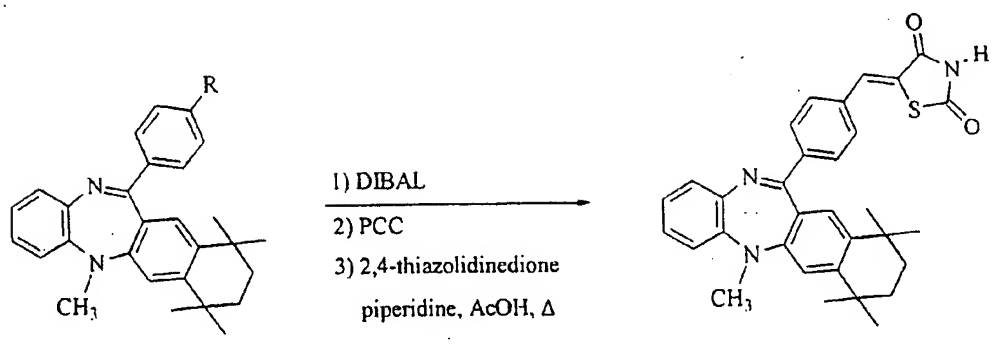
TZ195: Pale yellow plates (ethyl acetate / n-hexane); mp 233°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 7.69 (s, 1H), 7.39 (d, 2H, J = 8.1 Hz), 7.31 (d, 2H, J = 8.1 Hz), 7.26 (d, 2H, J = 8.8 Hz), 7.06 (dd, 1H, J = 8.4, 2.6 Hz), 6.83 (brs, 1H), 3.37 (s, 3H), 1.50 (m, 4H), 1.16 (s, 6H), 0.91 (s, 6H),
Anal. Calcd. for C26H28N2O3S, C= 69.62%, H= 6.29%, N= 6.24%,
Found C= 69.38%, H= 6.42%, N= 6.02%.

Example 19: Synthesis of TZ197.

It was synthesised (70 %) according to the process of Example 5 from thiazolidine III-2 (cf. Example 5) and 5,6,7,8-tetrahydro-N,5,5,8,8-pentamethyl-2-naphthylamine.

TZ197: Pale yellow prisms (ethyl acetate / n-hexane); mp 237°C
^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 7.59 (s, 1H), 7.48 (d, 1H, J = 7.0 Hz), 7.42 (m, 2H), 7.24 (d, 1H, J = 8.4 Hz), 7.19 (s, 1H), 7.04 (dd, 1H, J = 8.4, 2.2 Hz), 6.85 (d, 1H, J = 2.2 Hz), 3.41 (s, 3H), 1.51 (s, 4H), 1.14 (s, 6H), 0.91 (s, 6H),
Anal. Calcd. for C26H28N2O3S, C= 69.62%, H= 6.29%, N= 6.24%,
Found C= 69.51%, H= 6.37%, N= 6.27%.

Example 20: Synthesis of TZ201.



VII-1 R = $COOCH_3$
VII-2 R = CH_2OH
VII-3 R = CHO

TZ201

Ester body VII-1, 110mg (0.24 mmol) was dissolved in THF 10 mL, and DIBAL 1.5 mL (1M toluene solution, 1.5 mmol) was added at –20°C. 3 hours later, the reaction liquid was discharged into 2N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with Na_2SO_4, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : methylene chloride = 1 : 4) and compound VII-2 was obtained 100 mg (97 %).
^{1}H-NMR (400MHz, $CDCl_3$) 7.81 (d, 2H, J = 8.4 Hz), 7.40 (d, 2H, J = 8.4 Hz), 7.31 (d, 1H, J = 7.3 Hz), 7.13 (dt, 1H, J = 1-8,7.3 Hz), 7.08 (dt, 1H, J = 1.5, 7.3 Hz), 6.97 (dd, 1H, J = 1.5, 7.7 Hz), 6.94 (s, 1H), 6.92 (s, 1H), 4.77 (d, 2H, J = 4.4 Hz), 3.25 (s, 3H), 1.64 (m, 4H), 1.32 (s, 3H), 1.26 (s, 3H), 1.14 (s, 3H), 1.05 (s, 3H).

Compound VII-2, 100mg (0.24 mmol) was dissolved in methanol-free methylene chloride 10 ml, and PCC 60mg (0.28 mmol) was added and the mixture was stirred at room temperature for one hour. The reaction liquid was concentrated, and it was purified by silica gel column chromatography (ethyl acetate : methylene chloride = 1 : 50) and compound VII-3 was obtained 72 mg (72 %).

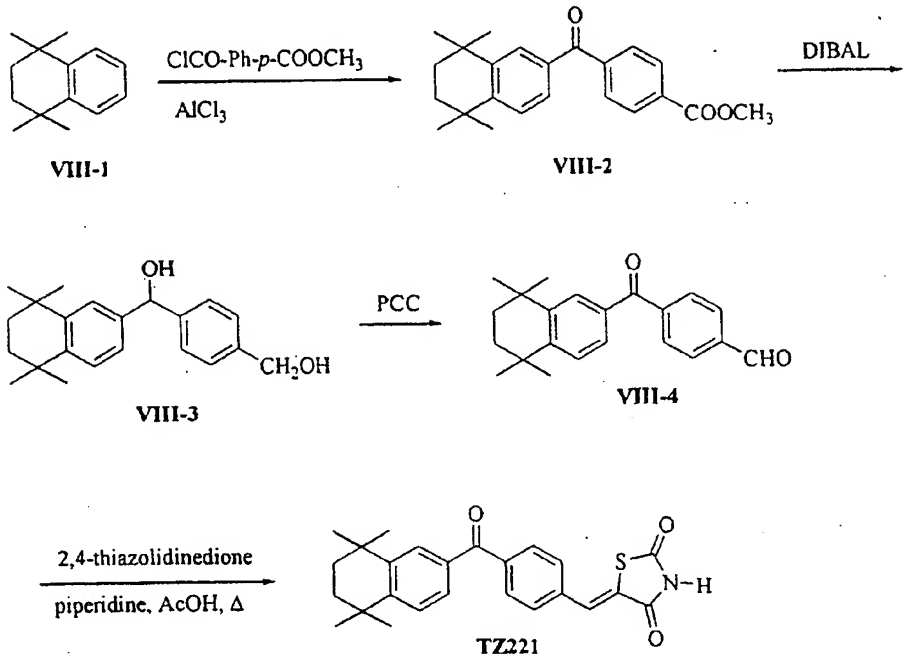
^{1}H-NMR (400MHz, $CDCl_3$) 10.10 (2, 1H), 7.98 (d, 2H, J= 8.0Hz), 7.92 (d, 2H, J = 8.8 Hz), 7.32 (d, 1H, J = 7.7 Hz), 7.17 (dt, 1H, J = 1.5, 8.0 Hz), 7.10 (dt, 1H, J = 1.5, 7.7 Hz), 6.98 (dd, 1H, J = 1.5, 8.1 Hz), 6.93 (s, 1H), 6.86 (s, 1H), 3.26 (s, 3H), 1.65 (m, 4H), 1.32 (s, 3H), 1.27 (s, 3H), 1.12 (s, 3H), 1.04 (s, 3H).

Compound VII-3, 70mg (0.17 mmol), 2,4-thiazolidinedione 20 mg (0.17 mmol) were suspended in anhydrous toluene 4 ml. Piperidine 173 µl and acetic acid 100 µl were dissolved in anhydrous toluene 25 ml, and the solution 2.5 ml thereof was added, and it was refluxed at 120°C for two hours. The reaction liquid was discharged into iced water and extraction was carried out with ethyl

acetate. The organic layer was washed with 2N hydrochloric acid, water, and it was dewatered with Na_2SO_4, and thereafter the solvent was concentrated, and TZ201 was obtained 73 mg (84 %).

TZ201: Red needles (ethyl acetate / methanol); mp >300°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 12.62 (s, 1H), 7.83 (s, 1H), 7.82 (d, 2H, J = 8.7 Hz), 7.69 (d, 2H, J = 8.3 Hz), 7.16-7.22 (m, 2H), 7.09 (m, 2H), 7.06 (s, 1H), 6-90 (s, 1H), 3.21 (s, 3H), 1.62 (m, 4H), 1.30 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H), 1.03 (s, 3H),
Anal. Calcd. for C32H31N3O2S•H2O, C= 71.23%, H= 6.16%, N= 7.79%,
Found C= 71.12%, H= 6.02%, N = 7.71 %.

Example 21: Synthesis of TZ221.



1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (VIII-1) 1.00 g (5.32 mmol) and terephthalic acid monomethyl ester chloride 1.06 g (5.32 mmol) were dissolved in methanol-free methylene chloride 20 ml, and aluminum chloride 1.42 g (10.64 mmol) was added under ice cooling, and thereafter it was refluxed for 30 minutes. The reaction liquid was discharged into iced water and extraction was carried out with ethyl acetate. The organic layer was washed with water, aqueous sodium chloride, and it was dewatered with $MgSO_4$ and thereafter, it was concentrated, thereafter, it was purified by silica gel column chromatography (ethyl acetate : hexane = 1 : 20 then 1 : 10), and thereby compound VIII-2 was obtained 1.3 g (70 %).

^{1}H-NMR (400 MHz, $CDCl_3$) 8.14 (d, 2H, J = 8.4 Hz), 7.83 (d, 2H, J = 8.4 Hz), 7.78 (d, 1H, J = 1.8 Hz), 7.53 (dd, 1H, J = 8.4, 1.8 Hz), 7.40 (d, 1H, J = 8.0 Hz), 3.97 (s, 3H), 1.72 (s, 4H), 1.32 (s, 6H), 1.29 (s, 6H).

Compound VIII-2, 1.20 g (3.43 mmol) was dissolved in THF 15 mL under argon replacement, and DIBAL 13.7 mL (1M toluene solution, 13.7 mmol) was added dropwise while stirring at –78°C. One hour was allowed to pass, and the reaction liquid was discharged into 1N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : hexane = 1 : 3) and as a result, because compound in which only ketone had been reduced (937.5 mg) was obtained, it was reduced by DIBAL again at 0°C for 30 minutes, the same post-treatment was carried out, and compound VIII-3 was obtained 896 mg (81 %).
^{1}H-NMR (400MHz, $CDCl_3$) 7.40 (d, 2H, J = 8.1 Hz), 7.34 (m, 3H), 7.25 (d, 1H, J = 8.0 Hz), 7.05 (dd, 1H, J = 8.0, 1.8 Hz), 5.80 (s, 1H), 4.68 (s, 2H), 2.15 (brs, 1H), 1.67 (s, 4H), 1.26 (s, 6H), 1.25 (s, 6H).

Alumina 4.70g and PCC 2.65 g (12.3 mmol) were suspended in methanol-free methylene chloride 10 ml under argon replacement, and compound VIII-3, 810mg (2.50 mmol) was dissolved in methanol-free methylene chloride 10 ml, and it was added gradually. 1 hour was allowed to pass, and thereafter the reaction liquid was concentrated, and it was purified using silica gel column chromatography (ethyl acetate : n-hexane = 1 : 7) and compound VIII-4 was obtained 798 mg (99.7 %).
^{1}H-NMR (400MHz, $CDCl_3$) 10.14 (s, 1H), 8.00 (d, 2H, J = 8.4 Hz), 7.91 (d, 2H, J = 8.1 Hz), 7.80 (d, 1H, J = 1.8 Hz), 7.53 (dd, 1H, J = 8.4, 2.2 Hz), 7.41 (d, 1H, J = 8.1 Hz), 1.73 (s, 4H), 1.32 (s, 6H), 1.30 (s, 6H).

Compound VIII-4, 790mg (2.47 mmol), 2,4-thiazolidinedione 319 mg (2.72 mmol) were suspended in anhydrous toluene 20 ml, and a solution of piperidine 63 mg (0.74 mmol) and acetic acid 45 mg (0.74 mmol) dissolved in anhydrous toluene 8 ml was added, and the mixture was refluxed at 120°C for three hours. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : hexane = 1 : 2) and TZ221 was obtained 328 mg (32 %).

TZ221: Colorless powder (ethyl acetate / n-hexane); mp 204°C

^{1}H-NMR (400MHz, $CDCl_3$) 8.46 (s, 1H), 7.90 (d, 2H, J = 8.4 Hz), 7.80 (d, 1H, J = 1.8 Hz), 7.60 (d, 2H, J = 8.1 Hz), 7.53 (dd, 1H, J = 8.0, 1.8 Hz), 7.41 (d, 1H, J = 8.1 Hz), 1.73 (s, 4H), 1.33 (s, 6H), 1.31 (s, 6H),
Anal. Calcd. for C25H25NO3S, C, 71.57, H, 6.01%; N, 3.34%,
Found, C, 71.28%;H, 5.92%; N, 3.09%.

Example 22: Synthesis of TZ223.
1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (VIII-1) and isophthalic acid monomethyl ester chloride were used as starting materials. TZ223 was synthesised according to the process of Example 21.

TZ223: Yellow prisms (ethyl acetate / n-hexane); mp 189°C; ^{1}H-NMR1R (400 MHz, $CDCl_3$) 8.46 (brs, 1H), 7.91 (s, 1H), 7.90 (s, 1H), 7.86 (d, 1H, J = 7.7 Hz), 7.81 (d, 1H, J = 1.8 Hz), 7.70 (d, 1H, J = 7.7 Hz), 7.61 (t, 1H, J = 7.7 Hz), 7.52 (dd, 1H, J = 8.1, 1.8 Hz), 7.42 (d, 1H, J = 8.1 Hz), 1.73 (s, 4H), 1.33 (s, 6H), 1.31 (s, 6H),
Anal. Calcd. for C25H25NO3S, C= 71.57%, H= 6.01%, N= 3.34%,
Found, C= 71.64%, H= 6.16%, N= 3.19%.

Example 23: Synthesis of TZ225.
1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl naphthalene and terephthalic acid monomethyl ester chloride were used as starting materials. TZ225 was synthesised according to the process of Example 21.

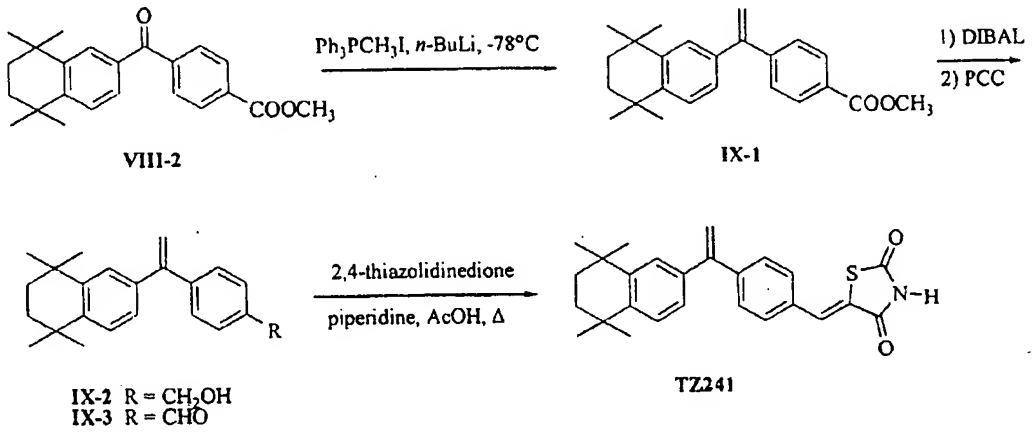
TZ225: Yellow prisms (ethyl acetate / n-hexane); mp 245°C
^{1}H-NMR (400MHz, $CDCl_3$) 8.67 (s, 1H), 7.91 (d, 1H, J = 8.4 Hz), 7.90 (s, 1H), 7.58 (d, 1H, J = 8.8 Hz), 7.26 (s, 1H), 7.21 (s, 1H), 2.33 (s, 3H), 1.70 (s, 4H), 1.32 (s, 6H), 1.22 (s, 6H),
Anal. Calcd. for C25H27NO3S, C= 72.03%, H= 6.28%, N= 3.23%,
Found, C= 71.87%, H= 6.35%, N = 3.14 %.

Example 24: Synthesis of TZ227.
1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl naphthalene and isophthalic acid monomethyl ester chloride were used as starting materials. TZ227 was synthesised according to the process of Example 21.

TZ227: Pale yellow prisms (ethyl acetate / n-hexane); mp 191°C
^{1}H-NMR (400MHz, $CDCl_3$) 8.40 (s, 1H), 7.87-7.92 (m, 2H), 7.86 (s, 1H), 7.69 (d, 1H, J = 7.7 Hz), 7.59 (t, 1H, J = 7.7 Hz), 7.25 (s, 1H), 7.23 (s, 1H), 2.32 (s, 3H), 1.71 (s, 4H), 1.33 (s, 6H), 1.22 (s, 6H),

Anal. Calcd. for C26H2NO3S, C= 72.03%, H= 6.28%, N= 3.23%,
Found, C= 72.21%, H= 6.37%, N= 2.96%.

Example 25: Synthesis of TZ241.



VIII-2 IX-1

IX-2 R = CH_2OH
IX-3 R = CHO

TZ241

Ph_3PCH_3I 4.04 g (10.1 mmol) was suspended in 5 mL of THF and n-butyllithium 8.36 ml (13.4 mmol) was added at –78°C and was stirred for 15 minutes. Compound VIII-2, 2.35 g (6.71 mmol) was dissolved in 12 mL of THF, and it was added and the mixture was stirred for one hour. Water was added to the reaction liquid, and extraction was carried out with methylene chloride. The organic layer was dewatered with $MgSO_4$, and thereafter, it was concentrated, and it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 12.5) and compound IX-1 was obtained 680 mg (30 %).

^{1}H-NMR (400 MHz, $CDCl_3$) 8.00 (d, 2H, J = 8.6 Hz), 7.43 (d, 2H, J = 8.4 Hz), 7.26 (d, 1H, J = 8.1 Hz), 7.22 (d, 1H, J = 1.8 Hz), 7.07 (dd, 1H, J = 8.3, 2.2 Hz), 5.53 (d, 1H, J = 1.1 Hz), 5.47 (d, 1H, J = 1.1 Hz), 3.93 (s, 3H), 1.69 (s, 4H), 1.30 (s, 6H), 1.23 (s, 6H).

Compound IX-1, 675 mg (2.01 mmol) was dissolved in THF 5 mL, and DIBAL 6.0 mL (1M toluene solution, 6.0 mmol) was added gradually at – 78°C, and thereafter it was stirred at 0°C for 30 minutes. The reaction liquid was discharged into 1N hydrochloric acid and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and it was dewatered with $MgSO_4$ and thereafter, it was concentrated and thereafter, purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and Compound IX-2 was obtained 619 mg (quantitative).

^{1}H-NMR (400MHz, $CDCl_3$) 7.35 (m, 4H), 7.27 (d, 1H, J = 1.8 Hz), 7.25 (d, 1H, J = 8.4 Hz), 7.08 (dd, 1H, J = 8.4, 2.2 Hz), 5.44 (d, 1H, J = 1.5 Hz), 5.40 (d, 1H, J = 1.1 Hz), 4.72 (s, 2H), 1.69 (s, 4H), 1.29 (s, 6H), 1.24 (s, 6H).

Compound IX-2, 620 mg (2.01 mmol) was dissolved in methanol-free methylene chloride 10 ml, and PCC 866mg (4.02 mmol) was added and the mixture was stirred at room temperature for one hour 30 minutes. The reaction liquid was concentrated, and it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and compound IX-3 was obtained 428.5 mg (70 %).

^{1}H-NMR (400MHz, $CDCl_3$) 10.03 (s, 1H), 7.85 (d, 2H, J = 8.4 Hz), 7.53 (d, 2H, J = 8.4 Hz), 7.27 (d, 1H, J = 8.1 Hz), 7.23 (d, 1H, J = 1.8 Hz), 7.06 (dd, 1H, J = 8.1, 1.8 Hz), 5.57 (d, 1H, J = 1.1 Hz), 5.51 (d, 1H, J = 0.7 Hz), 1.70 (s, 4H), 1.30 (s, 6H), 1.24 (s, 6H).

Compound XII-4, 420mg (1.37 mmol), 2,4-thiazolidinedione 162 mg (1.38 mmol) were sampled and suspended in anhydrous toluene 8 ml, and a solution of piperidine 32 mg (0.38 mmol) and acetic acid 23 mg (0.38 mmol) dissolved in anhydrous toluene 4 ml was added, and it was refluxed at 120°C for two hours. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and TZ241 was obtained 449.2 mg (81 %).

TZ241: Pale yellow needles (ethyl acetate / n-hexane); mp 198°C, ^{1}H-NMR (400 MHz, $CDCl_3$) 8.42 (s, 1H), 7.88 (s, 1H), 7.48 (m, 4H), 7.27 (d, 1H, J = 8.4 Hz), 7.24 (d, 1H, J = 1.8 Hz), 7.06 (dd, 1H, J = 8.4, 1.8 Hz), 5.52 (s, 1H), 5.51 (s, 1H), 1.70 (s, 4H), 1.30 (s, 6H), 1.25 (s, 6H),
Anal. Calcd. for C26H27NO2S, C= 74.79%, H= 6.52%, N= 3.35%,
Found C= 74.59%, H= 6.51%, N = 3-32%.

Example 26: Synthesis of TZ243.
m-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoyl) benzoic acid methyl ester was used as the starting material, and TZ243 was synthesised according to the process of Example 25.

TZ243: Colorless powder (ethyl acetate / n-hexane); mp 168°C
^{1}H-NMR (400MHz, $CDCl_3$) 8.30 (brs, 1H), 7.85 (s, 1H), 7.46 (m, 4H), 7.28 (d, 1H, J = 8.1 Hz), 7.25 (d, 1H, J = 2.2 Hz), 7.05 (dd, 1H, J = 8.1Hz, 2.2 Hz), 5.51 (d, 1H, J = 0..7 Hz), 5.46 (d, 1H, J = 1.1 Hz), 1.70 (s, 4H), 1.33 (s, 6H), 1.25 (s, 6H),
Anal. Calcd. for C26H27NO2S•1/4H2O, C= 74.00%, H= 6.57%, N= 3.32%,
Found C= 74.00%, H= 6.60%, N= 3.36%.

Example 27: Synthesis of TZ245.
Ph_3PCH_3I 1.09 g (2.70 mmol) was suspended in 5 mL of THF and n-butyllithium 2.22 ml (3.56 mmol) was added at -78°C and was stirred for 15 minutes. TZ225 (cf. Example 23) 800 mg (1.78

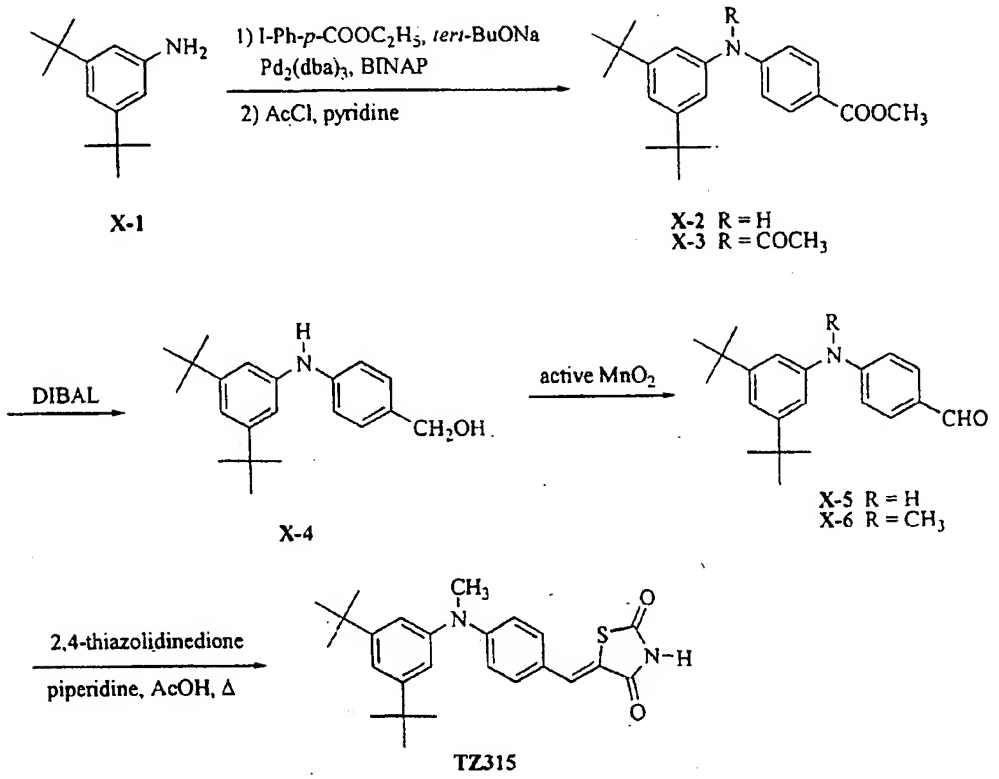
mmol) was dissolved in 6 mL of THF, and it was added and the mixture was stirred for one hour. Water was added to the reaction liquid and extraction was carried out with methylene chloride. The organic layer was dewatered with $MgSO_4$, and thereafter, it was concentrated, and it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and TZ245 was obtained 52 mg (6.5 %).

TZ245: Pale yellow powder (ethyl acetate / n-hexane); mp 281°C
^{1}H-NMR (400MHz, $CDCl_3$) 8.29 (s, 1H), 7.84 (s, 1H), 7.42 (m, 4H), 7.12 (s, 1H), 7.09 (s, 1H), 5.83 (d, 1H, J = 1.1 Hz), 5.32 (d, 1H, J = 1.1 Hz), 1.96 (s, 3H), 1.70 (s, 4H), 1.31 (s, 6H), 1.28 (s, 6H),
Anal. calcd. for C27H29NO2S, C= 75.14%, H= 6.77%, N= 3.25%,
Found C= 74.86%, H= 6.81%, N = 3.33 %.

Example 28: Synthesis of TZ247.
m-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthoyl) benzoic acid methyl ester was used as the starting material, and TZ247 was synthesised according to the process of Example 25.

TZ247: Pale yellow powder (ethyl acetate / n-hexane); mp 185°C, ^{1}H-NMR (400MHz, $CDCl_3$) 8.19 (brs, 1H), 7.79 (s, 1H), 7.49 (d, 1H, J = 7.7 Hz), 7.43 (t, 1H, J = 7.7 Hz), 7.37 (d, 1H, J = 7.7 Hz), 7.25 (s, 1H), 7.13 (s, 1H), 7.12 (s, 1H), 5.80 (d, 1H, J = 1.1 Hz), 5.31 (d, 1H, J = 1.1 Hz), 1.96 (s, 3H), 1.72 (s, 4H), 1.32 (s, 6H), 1.29 (s, 6H),
Anal. Calcd. for C27H29NO2S, C= 75.14%, H= 6.77%, N= 3.25%,
Found C= 74.85%, H= 6.72%, N= 2.98%.

Example 29: Synthesis of TZ315.



3,5-di-tert-butyl aniline (X-1) 1.00 g (4.88 mmol), 4-iodobenzoic acid ethyl 1.37 g (4.95 mmol), tert-BuONa 549mg (5.68 mmol) were dissolved in anhydrous toluene 15 ml, and, under argon replacement, tris (dibenzylideneacetone) dipalladium(0) 91 mg, (R)-BINAP 139mg (0.22 mmol) were introduced, and the mixture was stirred at 100°C for one hour. It was cooled to room temperature, and thereafter, extraction was carried out with ether. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 6) and Compound X-2 was obtained 0.94 g (55 %).

^{1}H-NMR (400MHz, $CDCl_3$) 7.92 (d, 2H, J = 8.8 Hz), 7.14 (t, 1H, J = 1.8 Hz), 7.02 (d, 2H, J = 1.8 Hz), 6.96 (d, 2H, J = 8.8 Hz), 4.33 (q, 2H, J = 7.3 Hz), 1.37 (t, 3H, J = 7.3 Hz), 1.32 (s, 18H).

Compound X-2, 935mg (2.65 mmol) was dissolved in anhydrous benzene 10 ml, and acetyl chloride 249 mg (3.18 mmol), anhydrous pyridine 0.5 ml were added, and the mixture was stirred at room temperature for five hours. Iced water was added to the reaction liquid, and extraction was carried out with ethyl acetate. The organic layer was washed with dilute hydrochloric acid, aqueous sodium chloride, and it was dewatered with $MgSO_4$, and after concentration, it was purified by

silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and Compound X-3 was obtained 956 mg (92 %).
^{1}H-NMR (400MHz, $CDCl_3$) 7.99 (d, 2H, J = 8.4 Hz), 7.39 (s, 1H), 7.34 (d, 2H, J = 8.8 Hz), 7.05 (d, 2H, J = 1.8 Hz), 4.35 (q, 2H, J = 7.3 Hz), 2.04 (s, 3H), 1.37 (t, 1H, J = 7.0 Hz), 1.30 (s, 18H).

Compound X-3, 950mg (2.40 mmol) was dissolved in THF 8 mL under argon replacement, and DIBAL 7.2 mL (1M toluene solution, 7.20 mmol) was added dropwise gradually while stirring at -78°C. The reaction liquid was discharged into 2N hydrochloric acid, and, after 15 minutes, extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and Compound X-4 was obtained 412 mg (55 %).
^{1}H-NMR (400MHz, $CDCl_3$) 7.27 (m, 3H), 7.04 (m, 3H), 6.96 (d, 2H, J = 1.5 Hz), 4.61 (s, 2H), 1.31 (s, 18H).

Compound X-4, 400mg (1.29 mmol) was dissolved in methanol-free methylene chloride 8 ml, and active MnO_2 1.32g (85 %, 12.9 mmol) was added, and the mixture was stirred at room temperature for 12 hours. The reaction liquid was filtered, thereafter the filtrate was concentrated, and it was purified by silica gel column chromatography (1 : 4) and Compound X-5 was obtained 184 mg (46 %).
^{1}H-NMR (400 MHz, $CDCl_3$) 9.78 (s, 1H), 7.74 (d, 2H, J = 8.8 Hz), 7.20 (t, 1H, J = 1.8 Hz), 7.05 (d, 1H, J = 1.8 Hz), 6.99 (d, 2H, J = 8.4 Hz), 6.17 (s, 1H), 1.33 (s, 18H).

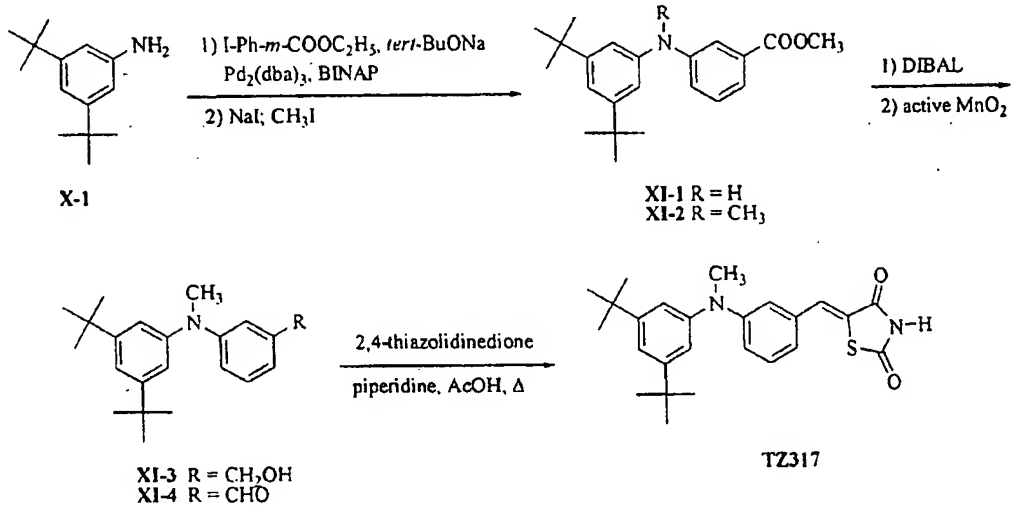
NaH 34mg (60 %, 0.87 mmol) was washed with n-hexane, and it was suspended in DMF 1 ml. Compound X-5, 180mg (0.58 mmol) was dissolved in DMF 5 ml, and it was added and the mixture was stirred at room temperature for 15 minutes. CH_3I 0.14 ml (2.25 mmol) was added to this mixture and further was stirred for one hour. The DMF was eliminated by distillation, and water was added to the residue and extraction was carried out with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 6) and Compound X-6 was obtained 173 mg (92 %).
^{1}H-NMR (400MHz, $CDCl_3$) 9.75 (s, 1H), 7.68 (d, 2H, J = 8.8 Hz), 7.33 (t, 1H, J = 1.8 Hz), 7.05 (d, 2H, J = 1.8 Hz), 6.74 (d, 2H, J = 8.8 Hz), 3.40 (s, 3H), 1.33 (s, 18H).

Compound X-6, 170mg (0.53 mmol) and 2,4-thiazolidinedione 62 mg (0.53 mmol) were suspended in anhydrous toluene 4 ml, and a solution of piperidine 13.4 mg (0.16 mmol) and acetic acid 9.5 mg (0.16 mmol) dissolved in anhydrous toluene 1.6 ml was added, and the mixture was refluxed at 120°C for one hour 30 minutes. The reaction liquid was discharged into iced water and extraction

was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and TZ315 was obtained 197 mg (89 %).

TZ315: Yellow needles (ethyl acetate / n-hexane); mp 254°C, ^{1}H-NMR (400MHz, $CDCl_3$) 8.11 (brs, 1H), 7.77 (s, 1H), 7.34 (m, 3H), 7.04 (d, 1H, J = 1.8 Hz), 6.77 (d, 2H, J = 8.8 Hz), 3.39 (s, 3H), 1.33 (s, 18H),
Anal. Calcd. for C25H30N2O2S, C= 71.06%, H= 7.16%, N= 6.63%;
Found C= 70.96%, H= 7.17%, N= 6.81%.

Example 30: Synthesis of TZ317.



3-iodobenzoic acid methyl 1.37 g (5.23 mmol), 3,5-di-tert-butyl aniline (X-1) 1.00 g (4.88 mmol), tert-BuONa 549mg (5.68 mmol) were dissolved in anhydrous toluene 15 ml, and, under argon replacement, tris (dibenzylideneacetone) dipalladium(0) 91 mg, (R)-BINAP 139mg (0.22 mmol) were introduced, and the mixture was stirred at 80°C for one hour. It was cooled to room temperature, and thereafter, it was extracted with ether. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and Compound XI-1 (crude product) was obtained 514 mg (31 %).
^{1}H-NMR (400MHz, $CDCl_3$) 7.87 (d, 1H, J = 7.7 Hz), 7.75 (m, 1H), 7.53 (m, 1H), 7.29 (t, 1H, J = 7.7 Hz), 7.07 (t, 1H, J = 1.5 Hz), 6.98 (d, 2H, J = 1.5 Hz), 3.88 (s, 3H), 1.32 (s, 18H).

NaH 88mg (60 %, 2.21 mmol) was washed with n-hexane, and it was suspended in DMF 1 ml. Compound XI-1 (crude product) 500 mg (1.47 mmol) was dissolved in DMF 8 ml, and it was added

and the mixture was stirred at room temperature for 15 minutes. Methyl iodide 0.35 ml (5.62 mmol) was added and the mixture was stirred for three hours. The DMF was eliminated by distillation, water was added to the residue and it was extracted with methylene chloride. The organic layer was washed in aqueous sodium chloride. It was dewatered with $MgSO_4$, thereafter, the solvent was eliminated by distillation, thereafter the residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 10) and Compound XI-2 was obtained 180 mg (34.5 %).
^{1}H-NMR (400MHz, CDCL3) 7.60 (m, 1H), 7.47 (d, 1H, J = 7.7 Hz), 7.23 (t, 1H, J = 8.0 Hz), 7.17 (t, 1H, J = 1.8 Hz), 7.04 (m, 1H), 6.99 (d, 2H, J = 1.8 Hz), 3.92 (s, 3H), 3.88 (s, 3H), 1.30 (s, 18H).

Compound XI-2, 170mg (0.48 mmol) was dissolved in THF 4 mL under argon replacement, and DIBAL 1.44 mL (1M toluene solution, 1.44 mmol) was added dropwise gradually while stirring at -78°C. After 30 minutes, it was discharged into 2N hydrochloric acid, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and Compound XI-3 was obtained 130 mg (83 %).
^{1}H-NMR (400 MHz, $CDCl_3$) 7.20 (t, 1H, J = 1.8 Hz) 7.14 (t, 1H, J = 1.8 Hz), 6.98 (d, 2H, J = 1.8 Hz), 6.92 (s, 1H), 6.81 (d, 2H, J = 8.1 Hz), 4.62 (d, 2H, J = 5.9 Hz), 3.34 (s, 3H), 1.30 (s, 18H).

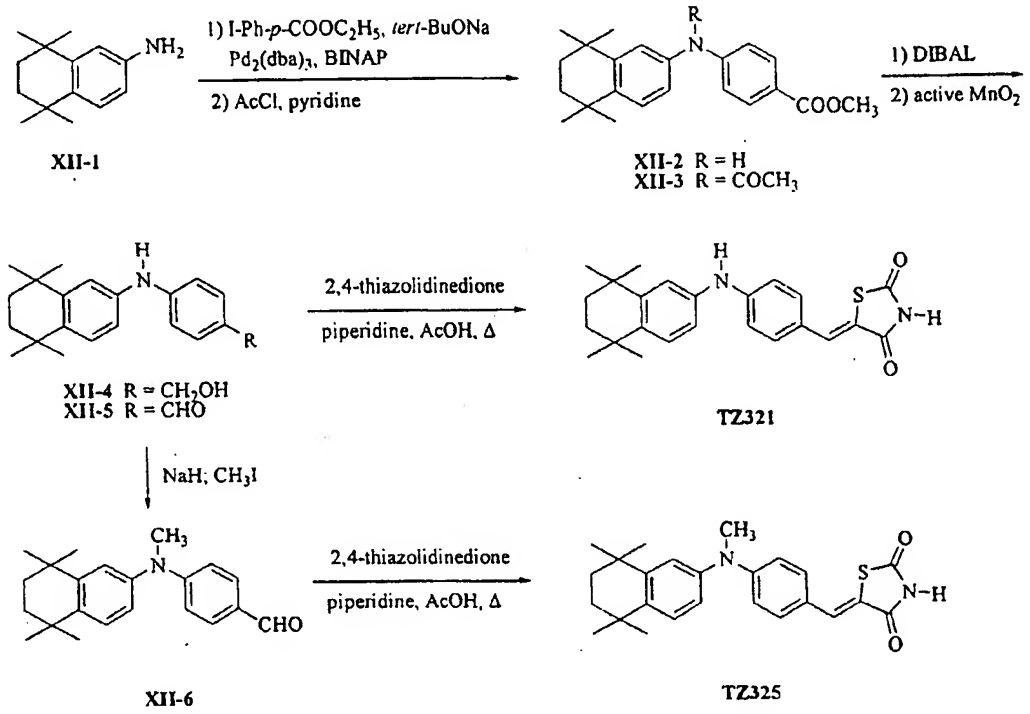
Compound XI-3, 125 mg (0.38 mmol) was dissolved in methanol-free methylene chloride 4 ml, and active MnO_2 394mg (85 %, 3.85 mmol) was added, and the mixture was stirred at room temperature for six hours 30 minutes. The reaction liquid was filtered, the filtrate was concentrated, thereafter, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 6) and Compound XI-4 was obtained 43.5 mg (35 %) (XI-3 is recovered 51 mg).
^{1}H-NMR (400MHz, $CDCl_3$) 9.92 (s, 1H), 7.35 (m, 1H), 7.32 (t, 1H, J = 7.7 Hz), 7.27 (m, 1H), 7.23 (t, 1H, J = 1.8 Hz), 7.07 (m, 1H), 7.02 (d, 1H, J = 1.8 Hz), 3.37 (s, 3H), 1.31 (s, 18H).

Compound XI-4, 65 mg (0.20 mmol), 2,4-thiazolidinedione 23 mg (0.20 mmol) were suspended in anhydrous toluene 3 ml. A solution of piperidine 5.1 mg (0.060 mmol) and acetic acid 3.6 mg (0.060 mmol) dissolved in anhydrous toluene 0.6 ml was added, and the mixture was refluxed at 120°C for three hours 30 minutes. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and thereafter the solvent was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and TZ317 was obtained 88 mg (quantitative).

TZ317: Yellow needles (ethyl acetate / n-hexane); mp 234°C

^{1}H-NMR (400MHz, $CDCl_3$) 8.41 (brs, 1H), 7.77 (s, 1H), 7.22-7.57 (m, 2H), 7.01 (d, 2H, J = 1.5 Hz), 6.89 (dd, 2H, J = 8.1, 2.2 Hz), 6.83 (t, 1H, J = 1.6 Hz), 3.35 (s, 3H), 1.32 (s, 18H),
Anal. Calcd. for C25H30N2O2S, C= 71.06%, H= 7.16%, N= 6.63%,
Found C= 70.88%, H= 7.09%, N = 6.36 %.

Example 31: Synthesis of TZ321.



2-amino-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene (XII-1) 1.50 g (7.39 mmol), 4-iodobenzoic acid ethyl 1.70 g (6.16 mmol), tert-BuONa 0.83 g (8.62 mmol) were dissolved in anhydrous toluene 30 ml, and, under argon replacement, tris (dibenzylideneacetone) dipalladium(0) 138 mg (0.15 mmol) and (R)-BINAP 210mg (0.33 mmol) were added to this mixture and stirred at 80°C. One hour was allowed to pass, the reaction liquid was cooled to room temperature and was extracted with ether, and the organic layer was washed with aqueous sodium chloride. It was dewatered with $MgSO_4$, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and Compound XII-2 was obtained 1.38 g (64 %).

^{1}H-NMR (400MHz, $CDCl_3$) 7.90 (d, 2H, J = 8.8 Hz), 7.26 (d, 2H, J = 8.4 Hz), 7.10 (d, 1H, J = 2.5 Hz), 6.96 (dd, 1H, J = 8.4, 2.6 Hz), 6.93 (d, 2H, J = 8.8 Hz), 4.33 (q, 2H, J = 7.0 Hz), 1.69 (s, 4H), 1.37 (t, 3H, J = 7.0 Hz), 1.28 (s, 6H), 1.27 (s, 6H).

Compound XII-2, 1.95 g (5.56 mmol) was dissolved in anhydrous pyridine 10 ml, and acetyl chloride 523 mg (6.67 mmol) was added and the mixture was stirred at room temperature for three hours. Iced water was added, and the mixture was extracted with ethyl acetate, and the organic layer was washed with dilute hydrochloric acid, aqueous sodium chloride. It was dewatered with $MgSO_4$, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and Compound XII-3 was obtained 1.34 g (61.5 %).
^{1}H-NMR (400MHz, $CDCl_3$) 8.00 (d, 2H, J = 8.4 Hz), 7.32 (d, 2H, J = 8.8 Hz), 7.31 (d, 1H, J = 8.8 Hz), 7.14 (d, 1H, J = 2.2 Hz), 6.95 (dd, 1H, J = 8.4, 2.2 Hz), 4.35 (q, 2H, J = 6.9 Hz), 2.05 (s, 3H), 1.69 (s, 4H), 1.37 (t, 3H, J = 6.9 Hz), 1.28 (s, 6H), 1.24 (s, 6H).

Compound XII-3, 1.34 g (3.41 mmol) was dissolved in THF 6 mL, and DIBAL 10.2 mL (1.0M toluene solution, 10.2 mmol) was added gradually at -78°C. 1 hour was allowed to pass, thereafter, it was discharged into 1N hydrochloric acid, and extraction was carried out with ethyl acetate. The organic layer was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and Compound XII-4 was obtained 621 mg (59 %).
^{1}H-NMR (400MHz, $CDCl_3$) 7.24 (d, 2H, J = 8.4 Hz), 7.03 (d, 1H, J = 2.2 Hz), 7.00 (d, 2H, J = 8.4 Hz), 6.89 (dd, 1H, J = 8.4, 2.2 Hz), 4.60 (s, 2H), 1.68 (s, 4H), 1.27 (s, 6H), 1.26 (s, 6H).

Compound XII-4, 615mg (2.0 mmol) was dissolved in methanol-free methylene chloride 8 ml, and active MnO_2 2.05g (85 %, 20.0 mmol) was added, and the mixture was stirred at room temperature for 16 hours. The reaction liquid was filtered, thereafter, the filtrate was concentrated, and it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and Compound XII-5 was obtained 271 mg (44 %).
^{1}H-NMR (400MHz, $CDCl_3$) 9.78 (s, 1H), 7.73 (d, 2H, J = 8.8 Hz), 7.29 (d, 1H, J = 8.4 Hz), 7.11 (d, 1H, J = 2.2 Hz), 6.99 (m, 3H), 1.70 (s, 4H), 1.29 (s, 6H), 1.28 (s, 6H).

Compound XII-5, 150mg (0.49 mmol) and 2,4-thiazolidinedione 63 mg (0.54 mmol) were suspended in anhydrous toluene 6 ml, and a solution of piperidine 12.7 mg (0.15 mmol) and acetic acid 8.9 mg (0.15 mmol) dissolved in anhydrous toluene 1.5 ml was added, and the mixture was refluxed at 120°C for 30 minutes. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, thereafter, it was concentrated, and TZ321 was obtained 178 mg (90 %).

TZ321: Orange needles (ethyl acetate / n-hexane); mp 297°C

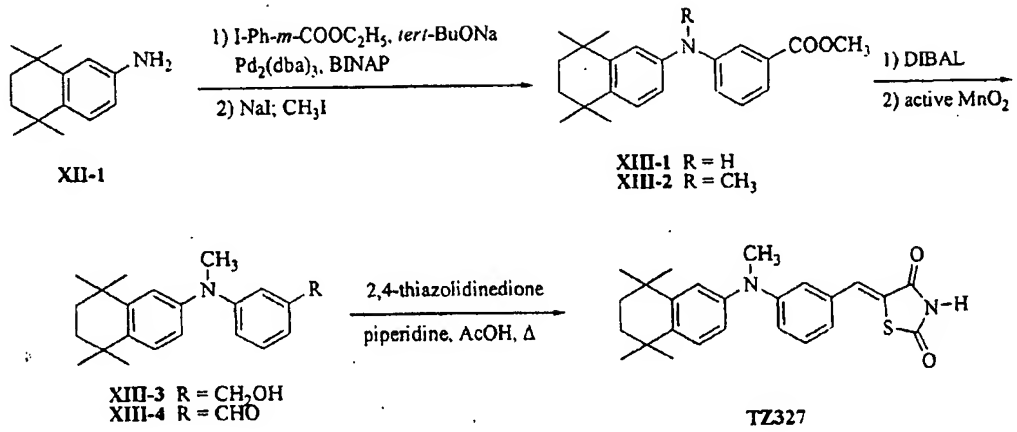
^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 8.69 (s, 1H), 7.65(S, 1H), 7.42 (d, 2H, J = 8.8 Hz), 7.26 (d, 1H, J = 8.8 Hz), 7.07 (d, 1H, J = 2.6 Hz), 7.06 (d, 2H, J = 8.4 Hz), 6.98 (dd, 1H, J = 8.4, 2.6 Hz), 1.64 (s, 4H), 1.24 (s, 6H), 1.24 (s, 6H),
Anal. Calcd. for C24H26N2O2S, C= 70.91%, H= 6.45%, N= 6.89%,
Found, C= 71.06%, H= 6.42%, N = 6.88 %.

Example 32: Synthesis of TZ325.
NaH 20mg (60 %, 0.49 mmol) was washed with little amount of n-hexane, and it was suspended in DMF 1 ml. Compound XII-5, 100mg (0.33 mmol) was dissolved in 4 mL of DMF and it was added to this suspension, and the mixture was stirred at room temperature for 20 minutes. CH_3I 0.08 mL (1.28 mmol) was added to this mixture, and the mixture was stirred for 30 minutes. DMF was distilled under reduced pressure and water was added to the residue and was extracted with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 5) and Compound XII-6 was obtained 80 mg (76.596).
^{1}H-NMR (400MHz, $CDCl_3$) 9.75 (s, 1H), 7.68 (d, 2H, J = 9.2 Hz), 7.34 (d, 1H, J = 8.4 Hz), 7.14 (d, 1H, J = 2.2 Hz), 6.96 (dd, 1H, J = 8.4, 2.2 Hz), 6.76 (d, 2H, J = 9.2 Hz), 3.37 (s, 3H), 1.71 (s, 4H), 1.31 (s, 6H), 1.26 (s, 6H).

Compound XII-6, 75mg (0.23 mmol), 2,4-thiazolidinedione 30 mg (0.26 mmol) were suspended in anhydrous toluene 4 ml, and a solution of piperidine 6.0 mg (0.07 mmol) and acetic acid 12 mg (0.07 mmol) dissolved in anhydrous toluene 0.75 ml was added, and the mixture was refluxed at 120°C. The reaction liquid was discharged into iced water, and, after 30 minutes, extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and it was dewatered at $MgSO_4$, and thereafter, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and TZ325 was obtained 105 mg (quantitative).

TZ325: Yellow powder (ethyl acetate / n-hexane); mp 238°C
^{1}H-NMR (400MHz, $CDCl_3$) 8.29 (s, 1H), 7.77 (s, 1H), 7.33 (d, 2H, J = 8.2 Hz), 7.33 (d, 1H, J = 8.4 Hz), 7.13 (d, 1H, J = 2.6 Hz), 6.95 (dd, 1H, J = 8.4, 2.6 Hz), 6.79 (d, 2H, J = 8.8 Hz), 3.36 (s, 3H), 1.71 (s, 4H), 1.31 (s, 6H), 1.26 (s, 6H),
Anal. Calcd. for C25H28N2O2S, C= 71.40%, H= 6.71%, N= 6.66%,
Found, C= 71.51%, H= 6.70%, N = 6.60 %.

Example 33: Synthesis of TZ327.



3-iodobenzoic acid methyl 1.24 g (4.73 mmol), 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylamine 1.03 g (5.07 mmol), tert-BuONa 571mg (5.92 mmol) were dissolved in anhydrous toluene 30 ml, and, under argon replacement, tris (dibenzylideneacetone) dipalladium(0) 117 mg (0.13 mmol), (R)-BINAP 177mg (0.28 mmol) were introduced, and the mixture was stirred at 80°C for one hour. The reaction liquid was cooled to room temperature, and extraction was carried out with ether. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and Compound XIII-1 was obtained 877 mg (55 %).

^{1}H-NMR (400MHz, $CDCl_3$) 7.70 (t, 1H, 2.0 Hz), 7.50 (d, 1H, J = 7.7 Hz), 7.28 (t, 1H, J = 7.9 Hz), 7.23 (d, 1H, J = 8.4 Hz), 7.17 (dd, 1H, JI8.1, 1.5 Hz), 7-O6 (d, 1H, J= 2-2 Hz), 6-90 (dd, 1H, J = 8.4, 2.2 Hz), 3.89-(s, 3H), 1.69 (s, 4H), 1.28 (s, 6H), 1.27 (s, 6H).

NaH 72mg (60 %, 1.78 mmol) was washed with n-hexane, and it was suspended in dried DMF 1 ml, and Compound XIII-1, 400mg (1.19 mmol) was dissolved in DMF 10 ml, and it was added, and the mixture was stirred at room temperature. After 20 minutes, methyl iodide 0.28 ml (4.50 mmol) was added, and the mixture was stirred for 40 minutes. The DMF was eliminated by distillation and water was added and the mixture was extracted with methylene chloride. The organic layer was washed with aqueous sodium chloride, and after elimination of the solvent, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and Compound XIII-2 was obtained 371.5 mg (94.5 %).

^{1}H-NMR (400MHz, $CDCl_3$) 7.60 (t, 1H, 2.0 Hz), 7.47 (d, 1H, 7.7 Hz), 7.25 (d, 1H, 8.4 Hz), 7.22 (d, 1H, 7.7 Hz), 7.08 (d, 1H, 2.6 Hz), 7.05 (dd, 1H, 8.4, 2.7 Hz), 6.88 (dd, 1H, 8.4Hz, 2.6 Hz), 3.88 (s, 3H), 3.33 (s, 3H), 1.68 (s, 4H), 1.29 (s, 6H), 1.24 (s, 6H).

Compound XIII-2, 570mg (1.62 mmol) was dissolved in THF 7 mL under argon replacement, and DIBAL 4.87 mL (1M toluene solution, 4.87 mmol) was added dropwise gradually while stirring this solution at −78°C. The reaction liquid was discharged into 2N hydrochloric acid, and, after 30 minutes, extraction was carried out with ethyl acetate. The organic layer was washed with 2N hydrochloric acid, saturated aqueous sodium bicarbonate solution, aqueous sodium chloride, and it was dewatered with $MgSO_4$, and after concentration, purification was carried out by silica gel column chromatography (1 : 3) and Compound XIII-3 was obtained 500 mg (91 %).

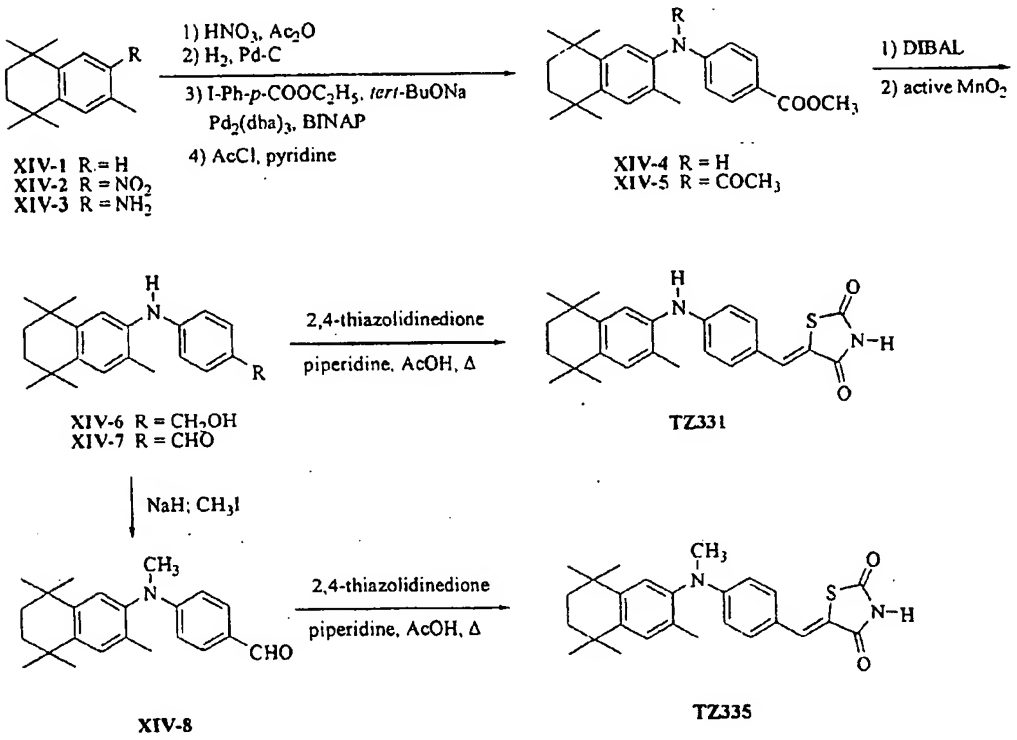
^{1}H-NMR (400MHz, $CDCl_3$) 7.23 (d, 1H, 8.3 Hz), 7.19 (d, 1H, 8.1 Hz), 7.06 (d, 1H, 2.6 Hz). 6.94 (m, 1H), 6.88 (dd, 1H, 8.4, 2.2 Hz), 6.84 (m, 2H), 4.62 (s, 2H), 3.31 (s, 3H), 1.68 (s, 4H), 1.29 (s, 6H), 1.24 (s, 6H).

Compound XIII-3, 100mg (0.30 mmol) was dissolved in methanol-free methylene chloride 4 ml, and active MnO_2 303mg (85 %, 2.97 mmol) was added, and the mixture was stirred at room temperature for 24 hours. The reaction liquid was filtered, and filtrate was concentrated, and thereafter, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 9) and Compound XIII-4 was obtained 71.6 mg (72 %).
^{1}H-NMR (400MHz, $CDCl_3$) 9.92 (s, 1H), 7.27-7.38 (m, 4H), 7.10 (d, 1H, 2.6 Hz), 7.06-7.09 (m, 1H), 6.92 (dd, 1H, 8.4, 2.2 Hz), 3.34 (s, 3H), 1.69 (s, 4H), 1.30 (s, 6H), 1.24 (s, 6H).

Compound XIII-4, 220mg (0.66 mmol), 2,4-thiazolidinedione 84 mg (0.72 mmol) were suspended in anhydrous toluene 6 ml, and a solution of piperidine 17 mg (0.20 mmol) and acetic acid 12 mg (0.20 mmol) dissolved in anhydrous toluene 2 ml was added, and the mixture was refluxed at 120°C for one hour. The reaction liquid was discharged into iced water and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and TZ327 was obtained 312 mg (quantitative).

TZ327: Orange prisms (ethyl acetate / n-hexane); mp 196°C,
^{1}H-NMR (400MHz, $CDCl_3$) 8.39 (s, 3H)7.76 (s, 3H) 7.31 (d, 1H, 8.4 Hz) 7.27 (d, 1H, 8.4 Hz) 7.10 (d, 1H, 2.2 Hz) 6.92 (dd, 1H, 8.4Hz, 2.2 Hz) 6.89 (d, 2H, 7.0 Hz) 6.83 (t, 1H, 2.0 Hz) 3.32 (s, 3H) 1.71 (s, 4H) 1.31 (s, 6H) 1.26 (s, 6H),
Anal. Calcd. for C25H28N2O2S, C= 71.40%, H= 6.71%, N= 6.66%,
Found, C= 71.15%, H= 6.61%, N = 6.44 %.

Example 34: Synthesis of TZ331.



1,2,3,4-tetrahydro-1,1,4,4,6-pentamethyl naphthalene 2.69 g (13.3 mmol) was dissolved in acetic anhydride 20 ml, and it was cooled to 0°C. 61 % nitric acid 0.74 ml (16.0 mmol) was added gradually to this solution. 2 hours were allowed to pass, and thereafter the reaction liquid was discharged into iced water, it was neutralized with sodium hydroxide, and thereafter, extraction was carried out with ether. The organic layer was shaken with aqueous sodium chloride and dewatered with $MgSO_4$, thereafter, it was concentrated, and Compound XIV-2 was obtained 3.03 g (92 %).

^{1}H-NMR (400 MHz, $CDCl_3$) 7.96 (s, 1H), 7.21 (s, 1H), 2.56 (s, 3H), 1.70 (s, 4H), 1.30 (s, 6H), 1.29 (s, 6H)

Compound XIV-2, 3.02 g (12.2 mmol) was dissolved in ethyl acetate 20 ml, ethanol 30 ml, and Pd/C 400 mg was added, and catalytic reduction was carried out with hydrogen at room temperature. Six hours 30 minutes was allowed to pass, thereafter, catalyst was eliminated by filtration, and filtrate was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and Compound XIV-3 was obtained 1.48 g (56 %).

^{1}H-NMR (400MHz, $CDCl_3$) 6.97 (s, 1H), 6.61 (s, 1H), 3.45 (brs, 2H), 2.14 (s, 3H), 1.64 (s, 4H), 1.24 (s, 6H), 1.24 (s, 6H).

4-iodobenzoic acid methyl 3.82 g (13.8 mmol), Compound XIV-3, 3.00 g (13.8 mmol) and tert-BuONa 1.55 g (16.1 mmol) were dissolved in anhydrous toluene 30 ml, and, under argon replacement, tris (dibenzylideneacetone) dipalladium(0) 320 mg (0.35 mmol), (R)-BINAP 480mg (0.77 mmol) were added, and the mixture was stirred at 100°C for three hours. The reaction liquid was cooled to room temperature and extraction was carried out with ether. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 10) and Compound XIV-4 was obtained 2.04 g (40 %).

^{1}H-NMR (400MHz, $CDCl_3$) 7.89 (d, J = 8.8Hz, 2H), 7.21 (s, 1H), 7.18 (s, 1H), 6.76 (d, J = 8.8Hz, 2H), 4.32 (q, J = 7.0Hz, 2H), 2.19 (s, 3H), 1.68 (s, 4H), 1.37 (t, J = 7.0 Hz, 3H), 1.29 (s, 6H), 1.24 (s, 6H).

Compound XIV-4, 2.03 g (5.56 mmol) was dissolved in anhydrous benzene 30 ml, and acetyl chloride 524 mg (6.67 mmol) and anhydrous pyridine 1 ml were added, and the mixture was stirred at room temperature for two hours. Acetyl chloride 0.20 ml was further added to the reaction liquid and it was stirred at 50°C for four hours and furthermore at 60°C for 23 hours. Iced water was added to the reaction liquid and extraction was carried out with ethyl acetate. The organic layer was washed with 2N hydrochloric acid and aqueous sodium chloride, and it was dewatered with $MgSO_4$, and thereafter, it was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and Compound XIV-5 was obtained 1.66 g (62 %).

^{1}H-NMR (400MHz, $CDCl_3$) 7.97 (d, J = 8.8Hz, 2H), 7.33 (d, J = 8.8Hz, 2H), 7.17 (s, 1H), 7.13 (s, 1H), 4.34 (q, J = 7.0Hz, 2H), 2.06 (s, 3H), 1.97 (s, 3H), 1.69 (s, 4H), 1.36 (t, J = 7.0 Hz, 3H), 1.29 (s, 6H), 1.26 (s, 6H).

Compound XIV-5, 1.62 g (3.98 mmol) was dissolved in THF 10 mL under argon replacement, and DIBAL 11.9 mL (1M toluene solution, 11.9 mmol) was added slowly dropwise while stirring this solution at –78°C. After 30 minutes, the reaction liquid was discharged into 2N hydrochloric acid, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and Compound XIV-6 was obtained 0.99 g (77 %).

^{1}H-NMR (400MHz, $CDCl_3$) 7.23 (d, J = 8.4Hz, 2H), 7.19 (s, 1H), 7.12 (s, 1H), 6.87 (d, J = 8.4Hz, 2H), 5.33 (s, 1H), 4.60 (d, J = 5.5Hz, 2H), 2.20 (s, 3H), 1.67 (s, 4H), 1.51 (t, J = 5.6 Hz, 1H), 1.28 (s, 6H), 1.22 (s, 6H).

Compound XIV-6, 985mg (3.05 mmol) was dissolved in methanol-free methylene chloride 14 ml, and active MnO_2 3.11g (85 %, 30.5 mmol) was added, and the mixture was stirred at room

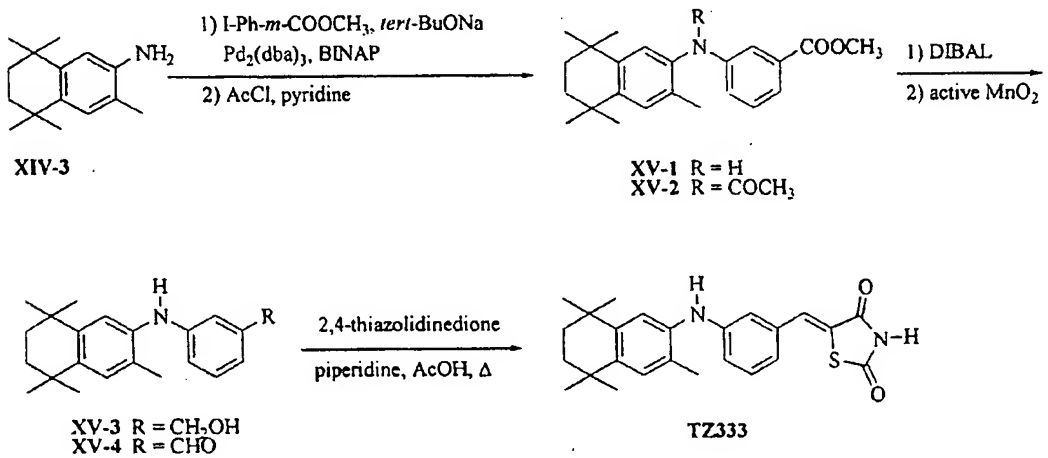
temperature for 22 hours. The reaction liquid was filtered, and the filtrate was concentrated, and thereafter, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and Compound XIV-6 was obtained 297 mg (30 %, raw material recovered 282 mg).

^{1}H-NMR (400MHz, $CDCl_3$) 9.76 (s, 1H), 7.71 (d, J = 8.8Hz, 2H), 7.20 (s, 1H), 7.18 (s, 1H), 6.78 (d, J = 8.4 Hz, 2H), 5.80 (s, 1H), 2.05 (s, 3H), 1.69 (s, 4H), 1.30 (s, 6H), 1.25 (s, 6H).

Compound XIV-6, 70mg (0.22 mmol), 2,4-thiazolidinedione 25.5 mg (0.22 mmol) were suspended in anhydrous toluene 4 ml, and a solution of piperidine 5.6 mg (0.065 mmol) and acetic acid 3.9 mg (0.065 mmol) dissolved in anhydrous toluene 0.67 ml was added, and the mixture was refluxed at 120°C for seven hours. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and TZ331 was obtained 72.5 mg (79 %).

TZ331: Yellow needles (methylene chloride/ n-hexane); mp 284°C;
^{1}H-NMR (400MHz, $CDCl_3$) 8.31 (brs, 1H), 7.77 (s, 1H), 7.36 (d, J = 8.8Hz, 2H), 7.19 (s, 1H), 7.17 (s, 1H), 6.81 (d, J = 8.8Hz, 2H), 5.74 (s, 1H), 2.19 (s, 3H), 1.69 (s, 4H), 1.29 (s, 6H), 1.25 (s, 6H),
Anal. Calcd. for C25H28N2O2S, C= 71.40%, H= 6.71%, N = 6.66 %.

Example 35: Synthesis of TZ333.



3-iodobenzoic acid methyl 1.77 g (6.77 mmol), Compound XIV-3, 1.47 g (6.77 mmol) and tert-BuONa 763mg (7.91 mmol) were dissolved in anhydrous toluene 15 ml, and, under argon replacement, tris (dibenzylideneacetone) dipalladium(0) 122 mg (0.14 mmol), (R)-BINAP 187mg

(0.30 mmol) were added, and the mixture was stirred at 100°C for two hours 30 minutes. The reaction liquid was cooled to room temperature, and extraction was carried out with ether. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and Compound XV-1 was obtained 1.45 g (61 %).
^{1}H-NMR (400MHz, $CDCl_3$) 7.59 (t, J = 2.0Hz, 1H), 7.48 (td, J = 7.7, 1.2Hz, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.20 (s, 1H), 7.14 (s, 1H), 7.04 (m, 1H), 5.42 (brs, 1H), 3.88 (s, 3H), 2.19 (s, 3H), 1.68 (s, 4H), 1.29 (s, 6H), 1.24 (s, 6H).

Compound XV-1, 1.44 g (4.10 mmol) was dissolved in anhydrous benzene 16 ml, and acetyl chloride 386 mg (4.92 mmol), anhydrous pyridine 1 ml were added, and the mixture was stirred at room temperature for two hours. Acetyl chloride 0.20 ml was added to the reaction liquid and the liquid was further stirred at 50°C for four hours and further at 70°C for six hours. Iced water was added to the reaction liquid and extraction was carried out with ethyl acetate. The organic layer was washed with 2N hydrochloric acid and aqueous sodium chloride, it was dewatered with $MgSO_4$, and thereafter, it was concentrated. The residue was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and Compound XV-2 was obtained 1.37 g (85 %).
^{1}H-NMR (400MHz, $CDCl_3$) 8.00 (s, 1H), 7.82 (m, 1H), 7.45 (td, J = 8.0, 2.2Hz, 1H), 7.37 (bt, J = 8.3 Hz, 1H), 7.19 (brs, 1H), 7.15 (s, 1H), 3.88 (s, 3H), 2.10 (s, 3H), 1.96 (s, 3H), 1.69 (s, 4H), 1.27 (s, 12H).

Compound XV-2, 1.37 g (3.49 mmol) was dissolved in THF 8 mL under argon replacement, and DIBAL 10.5 mL (1M toluene solution, 10.5 mmol) was added slowly dropwise while stirring at – 78°C. After 30 minutes, the reaction liquid was discharged into 2N hydrochloric acid, and extraction was carried out with ethyl acetate. The organic layer was washed with 2N hydrochloric acid and aqueous sodium chloride, and it was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and Compound XV-3 was obtained 0.91 g (81 %).
^{1}H-NMR (400MHz, $CDCl_3$) 7.21 (t, J = 7.7Hz, 1H), 7.20 (s, 1H), 7.12 (s, 1H), 6.92 (s, 1H), 6.82 (m, 2H), 5.35 (brs, 1H), 4.62 (d, J = 5.8Hz, 2H), 2.19 (s, 3H), 1.68 (s, 4H), 1.59 (t, J = 5.8 Hz, 1H), 1.28 (s, 6H), 1.23 (s, 6H).

Compound XV-3, 900mg (2.79 mmol) was dissolved in methanol-free methylene chloride 12 ml, and active MnO_2 2.86 g (85 %, 27.9 mmol) was added, and the mixture was stirred at room temperature for 15 hours. The reaction liquid was filtered, and the filtrate was concentrated, and thereafter, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 8) and Compound XV-4 was obtained 119 mg (13 %).

^{1}H-NMR (400MHz, $CDCl_3$) 9.92 (s, 1H), 7.37 (t, J = 7.7Hz, 1H), 7.31 (m, 2H), 7.18 (s, 1H), 7.15 (s, 1H), 7.09 (m, 1H), 5.48 (brs, 1H), 2.19 (s, 3H), 1.68 (s, 4H), 1.29 (s, 6H), 1.24 (s, 6H).

Compound XV-4, 115mg (0.36 mmol), 2,4-thiazolidinedione 84 mg (0.72 mmol) were suspended in anhydrous toluene 8 ml, and a solution of piperidine 9.2 mg (0.11 mmol) and acetic acid 6.4 mg (0.11 mmol) dissolved in anhydrous toluene 1.1 ml was added, and the mixture was refluxed at 120°C for seven hours. The reaction liquid was discharged into iced water, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and TZ333 was obtained 138 mg (92 %).

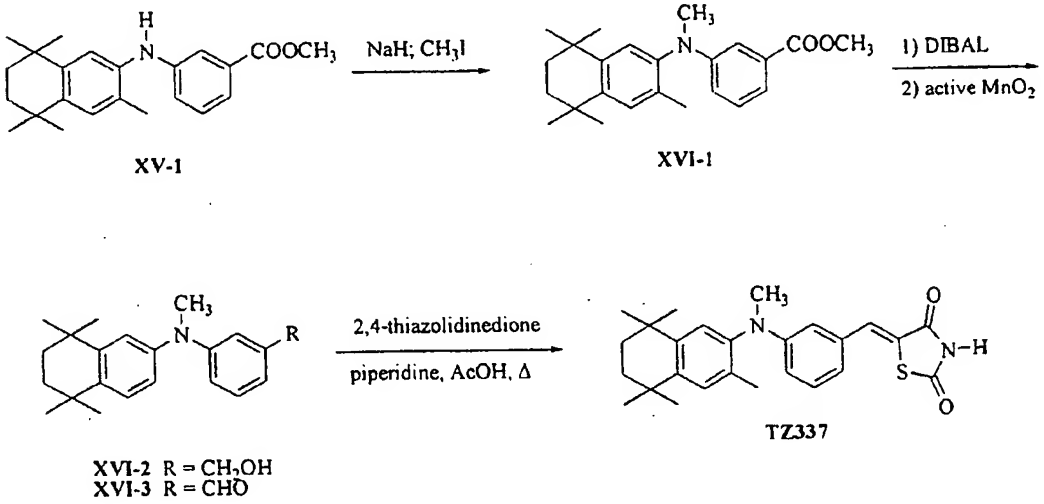
TZ333: Yellow needles (ethyl acetate / n-hexane); mp 223°C,
^{1}H-NMR (400MHz, $CDCl_3$) 8.29 (brs, 1H), 7.75 (s, 1H), 7.30 (t, J = 8.1Hz, 1H), 7.17 (s, 1H), 7.15 (s, 1H), 6.93 (m, 2H), 6.81 (m, 1H), 5.43 (s, 1H), 2.19 (s, 3H), 1.69 (s, 4H), 1.30 (s, 6H), 1.24 (s, 6H),
Anal. Calcd. for C25H28N2O2S, C= 71.40%, H= 6.71%, N= 6.66%,
Found, C= 71.20%, H= 6.76%, N= 6.65%.

Example 36: Synthesis of TZ335.
NaH 40mg (60 %, 1.01 mmol) was washed with little amount of n-hexane, and it was suspended in DMF 1 ml. XIV-7, 216mg (0.67 mmol) dissolved in 6 mL of DMF was added in this suspension, and the mixture was stirred at room temperature for 20 minutes. CH_3I 0.08 mL (1.35 mmol) was added to the reaction liquid, and the mixture was stirred time for 30 minutes. DMF was distilled under reduced pressure and water was added and the mixture was extracted with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 4) and XIV-8 was obtained 140 mg (62 %).
^{1}H-NMR (400MHz, $CDCl_3$) 9.73 (s, 1H), 7.67 (d, J = 8.1 Hz, 2H), 7.20 (s, 1H), 7.03 (s, 1H), 6.54 (brs, 2H), 3.30 (s, 3H), 2.04 (s, 3H), 1.69 (s, 4H), 1.31 (s, 6H), 1.23 (s, 6H).

XIV-8, 130mg (0.39 mmol), 2,4-thiazolidinedione 45 mg (0.39 mmol) were suspended in anhydrous toluene 6 ml, and a solution of piperidine 9.9 mg (0.12 mmol) and acetic acid 7 mg (0.12 mmol) dissolved in anhydrous toluene 1.2 ml was added, and the mixture was refluxed at 120°C. After six hours, the reaction liquid was discharged into iced water and extraction was carried out with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and TZ335 was obtained 145 mg (86 %).

TZ335: Yellow powder (methylene chloride / methanol); mp >300°C,
^{1}H-NMR (400MHz, DMSO-d_6,30°C) 12.30 (brs, 1H), 7.63 (S, 1H), 7.39 (d, J= 8.4HZ, 2H), 7.29 (s, 1H), 7.09 (s, 1H), 6.53 (d, J = 8.3Hz, 2H), 3.29 (s, 3H), 1.99 (s, 3H), 1.65 (s, 4H), 1.27 (s, 6H), 1.21 (s, 6H),
Anal. Calcd. for C26H30N2O2S, C= 71.86%, H= 6.96%, N= 6.45%,
Found, C= 71.60%, H= 6.99%, N = 6.67%.

Example 37: Synthesis of TZ337.



NaH 146mg (60 %, 3.65 mmol) was washed with little amount of n-hexane, and it was suspended in DMF 1 ml. XV-1, 855mg (2.44 mmol) was dissolved in 12 mL of DMF was added to this suspension, and the mixture was stirred at room temperature for 20 minutes. CH_3I 0.30 ml (4.87 mmol) was added to the reaction liquid, and the mixture was stirred for one hour. DMF was distilled under reduced pressure, water was added and the mixture was extracted with methylene chloride. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 10) and XVI-1 was obtained 788.5 mg (89 %).
^{1}H-NMR (400MHz, $CDCl_3$) 7.34 (d, J = 7.7Hz, 1H), 7.30 (m, 1H), 7.17 (s, 1H), 7.16 (t, J = 7.7Hz, 1H), 7.04 (s, 1H), 6.59 (dd, J = 7.4, 1.8 Hz, 1H), 3.88 (s, 3H), 3.25 (s, 3H), 2.04 (s, 3H), 1.68 (s, 4H), 1.30 (s, 3H), 1.22 (s, 3H).

XVI-1, 750mg (2.05 mmol) was dissolved in THF 7 mL under argon replacement, and DIBAL 6.16 mL (1M toluene solution, 6.16 mmol) was added dropwise gradually while stirring at –78°C. After 30 minutes, the reaction liquid was discharged into 2N hydrochloric acid, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and

was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 2) and XVI-2 was obtained 616 mg (89 %).
^{1}H-NMR (400MHz, $CDCl_3$) 7.16 (s, 1H), 7.14 (t, J = 7.7Hz, 1H), 7.04 (s, 1H), 6.68 (d, J = 7.3Hz, 1H), 6.58 (s, 1H), 6.41 (dd, J = 8.1, 2.2Hz, 1H), 4.60 (d, J = 5.8Hz, 2H), 3.22 (s, 3H), 2.06 (s, 3H), 1.68 (s, 4H), 1.52 (t, J = 5.9 Hz, 1H), 1.30 (s, 6H), 1.21 (s, 6H).

XVI-2, 610mg (1.81 mmol) was dissolved in methanol-free methylene chloride 8 ml, and active MnO_2 1.85g (85 %, 18.1 mmol) was added, and the mixture was stirred at room temperature for 30 hours. The reaction liquid was filtered, the filtrate was concentrated, and thereafter, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 10) and XV-3 was obtained 423 mg (70 %).
^{1}H-NMR (400MHz, $CDCl_3$) 9.91 (s, 1H), 7.28 (t, J = 7.3Hz, 1H), 7.18 (m, 2H), 7.07 (m, 1H), 7.04 (s, 1H), 6.69 (dd, J = 8.4, 2.6Hz, 1H), 3.26 (s, 3H), 2.05 (s, 3H), 1.69 (s, 4H), 1.31 (s, 6H), 1.22 (s, 6H).

XV-3, 415mg (1.24 mmol), 2,4-thiazolidinedione 145 mg (1.42 mmol) were suspended in anhydrous toluene 10 ml, and a solution of piperidine 32 mg (0.37 mmol) and acetic acid 22 mg (0.37 mmol) dissolved in anhydrous toluene 4 ml was added, and it was refluxed at 120°C. Six hours were allowed to pass, and the reaction liquid was discharged into iced water and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and was dewatered with $MgSO_4$, and after concentration, it was purified by silica gel column chromatography (ethyl acetate : n-hexane = 1 : 3) and TZ337 was obtained 504 mg (94 %).

TZ337: Orange crystals (ethyl acetate / n-hexane); mp 219°C
^{1}H-NMR (400MHz, $CDCl_3$) 8.22 (brs, 1H), 7.74 (s, 1H), 7.27 (t, J = 7.7Hz, 1H), 7.04 (s, 1H), 6.80 (d, J = 8.4Hz, 1H), 6.64 (dd, J = 8.0, 2.2Hz, 1H), 6.48 (s, 1H), 3.26 (s, 3H), 2.05 (s, 3H), 1.70 (s, 4H), 1.32 (s, 6H), 1.24 (s, 6H),
Anal. Calcd. for C26H30N2O2S, C= 71.86%, H= 6.96%, N= 6.45%;
Found, C= 71.65%, H= 7.16%, N= 6.75%.

Example 38: Test Example.
Using each compound of this invention, effect with respect to cell differentiation induction action when alone and cell differentiation induction action when retinoid was also present were examined. Am80 [4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl) carbamoyl] benzoic acid was used as retinoid which was also present to make comparison. Using promyelocytic leukemia cell strain HL-60, differentiation to granulocyte system was assessed by change of form and measured by ability to reduce nitroblue tetrazolium (NBT). The proportion of cells which had differentiated (%) as shown in the floowing table is calculated from the ability to reduce NBT.

(A) The concentration-dependence of the ability to induce differentiation inducibility of each compound individually and the concentration-dependent effect of 1 x 10^{-9}M Am80 was measured. TZ91 and TZ181 showed cell differentiation induction activity even alone, and furthermore,the activity of Am80, which was also present in a concentration where it did not exhibit cell differentiation induction activity, was strengthened. Moreover, TZ201 did not have activity on its own, but inhibited the activity of Am80 which is also present.

Table 1

	Proportion (%) of differentiated cells with compound alone				Proportion (%) of differentiated cells with 1x10^{-9}M Am80 also present				
Com-pound	concentration				concentration				
	-9	-8	-7	-6	None	-9	-8	-7	-6
TZ91	1.2	0.8	7	87	49	58	62	87	-
TZ181	-	1	7	54	37	-	53	58	6
TZ201	-	0.3	0.7	0.3	48	-	64	53	5

(B) Concentration-dependent differentiation inducibility with respect to each compound alone and concentration-dependent differentiation inducibility in the presence of 1x10^{-10}M Am80 was measured. TZ151 showed cell differentiation induction activity alone, and when Am80 was also present at a concentration at which it did not show cell differentiation induction activity, the activity was enhanced further. Moreover, neither TZ161 nor TZI91 have activity alone, but enhanced the activity of Am80 which was also present, and acted in an inhibitory manner at high concentration (1x10^{-6}M).

Table 2

	Proportion (%) of differentiated cells with compound alone			Proportion (%) of differentiated cells with 1x10^{-10}M Am80 also present			
Compound	concentration			concentration			
	-8	-7	-6	None	-8	-7	-6
TZ151	3	4.4	78	4	12	43	83
TZ161	3.5	1.8	3.6	4	12	25	3.8
TZ191	3.6	3.5	4.1	11	63	75	28

(C) Concentration-dependent differentiation inducibility with respect to each compound alone and concentration-dependent differentiation inducibility in the presence of 3x10^{-9}M Am80 was measured. All the aforesaid 5 compounds other than TZ241 showed cell differentiation induction activity alone, and when Am80 was also present at a concentration at which it did not show cell differentiation induction activity, further enhanced activity was was aobserved for all 5 compounds.

Table 3

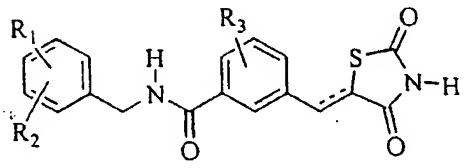
	Proportion (%) of differentiated cells with compound alone			Proportion (%) of differentiated cells with $1x10^{-9}$M Am80 also present			
Compound	concentration			concentration			
	-8	-7	-6	none	-8	-7	-6
TZ221	1.4	2	51	44	54	67	82
TZ241	2.8	6.4	89	44	76	84	92
TZ245	3.8	3	11	44	86	89	88
TZ321	1.2	1.1	28	51	55	83	88
TZ325	2.2	21	87	51	72	83	79

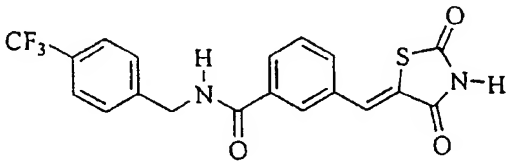
(D) Concentration of each compound was fixed at $1x10^{-6}$M, and effect with respect to concentration-dependent differentiation inducibility of retinoid (Am80) was measured. The aforesaid 4 compounds did not exhibit cell differentiation induction activity alone, and inhibited the activity of Am80 which was also present.

Table 4.

Compound	Retinoid also present (concentration)			
	none	Am80(-9)	Am80(-9.5)	Am80(-10)
none	1.5	80	53	8.5
TZ223	4.4	62	22	5
TZ227	5.3	11.7	5.5	7
TZ243	4.2	77	35	5
TZ247	7	10	5.8	6.4

(E) In Kokai 9-48771, it is demonstrated that N-benzyl dioxo thiazolidyl benzamide derivatives represented by following general formula have insulin resistance improvement action. Therefore, TZ105 was synthesised as an N-benzyl derivative for comparison, and examined for presence or absencde of retinoid activity.





TZ105

II-2 (Example 4) 150 mg (0.60 mmol) was suspended in anhydrous benzene 12 ml, and $SOCl_2$ 358mg (3.01 mmol) was added, and the mixture was refluxed for 14 hours. The $SOCl_2$ was eliminated by distillation, and thereafter the residue was suspended in anhydrous benzene 10 ml, and 4-trifluoro benzylamine 106 mg (0.60 mmol), anhydrous pyridine 1 ml were added, and the mixture was stirred at room temperature for one hour. To the reaction liquid was added 2N hydrochloric acid with ice floating, and extraction was carried out with ethyl acetate. The organic layer was washed with aqueous sodium chloride, and water was removed with $MgSO_4$, and thereafter, it was concentrated, and thereafter, purification was carried out by silica gel column chromatography (ethyl acetate : n-hexane = 3 : 2) and TZ105 was obtained 128 mg (52 %).

TZ105: Colorless needles (ethyl acetate /n-hexane); mp 204°C, ^{1}H-NMR (400 MHz, DMSO-d_6, 30°C) 9.23 (t, 1H, J = 5.9 Hz), 8.10 (s, 1H), 7.97 (d, 1H, J = 8.7 Hz), 7.83 (s, 1H), 7.76 (d, 1H, J = 8.7 Hz), 7.70 (d, 2H, J = 8.1 Hz), 7.65 (t, 1H, J = 7.7 Hz), 7.55 (d, 2H, J = 8.0 Hz), 4.59 (d, 2H, J= 5.9 Hz); Anal. Calcd. for C19H13N2O3SF3, C: 56.16%, H: 3.22%, N: 6.89%,
Found C: 56.36%, H: 3.04%, N: 6.98 %.

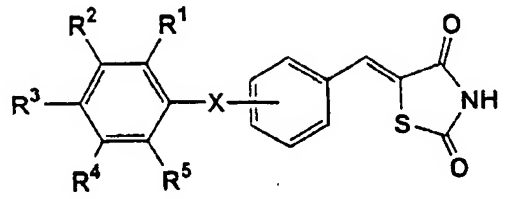
In assay system using HL-60 cell described above, TZ105 did not exhibit any differentiation induction activity at all, and also it did not exert any influence on the action of retinoid Am80 which was also present. Accordingly, retinoid or retinoid inhibition action is not displayed by the N-benzyl compound, and it is thought that in this structure, it is essential that a nitrogen atom is present in the aromatic ring, as in TZ185 and the like.

Possible Applications in Industry

Because the compounds of this invention display a retinoid-like activity or retinoid-like activity regulation by acting on retinoid receptor, (enhancement or inhibition of retinoid action), they are useful as effective ingredient of drug for prevention and/or therapy of disease such as cancer, diabetes mellitus, arteriosclerosis, bone disease, rheumatism or immunologic disease or the like.

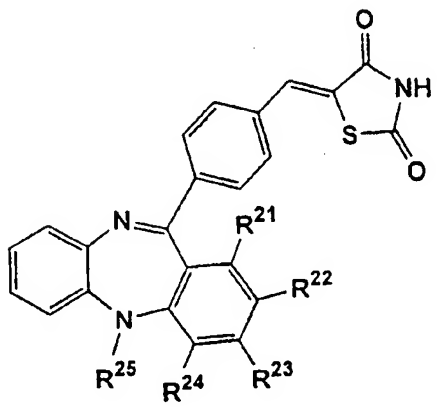
Patent Claims

1. A compound represented by the following general formula (I)



(wherein, R1, R2, R3, R4 and R5 each independently denote hydrogen atom or lower alkyl group, and among these, two adjacent groups, together with carbon atoms of phenyl ring that they are bonded to, may bond to form a 5-membered ring or 6-membered ring optionally having 1 or more alkyl groups; X denotes a group represented by -C(R6)=CH-, -CH=C(R7)-, -N(R8)-CO-, -CO-N(R9)-, -C(=CHR10), -CO- or -NR11- (wherein, R6, R7, R8, R9, R10 and R11 each independently denote hydrogen atom or lower alkyl group)), or

a compound represented by following general formula (II)



(wherein, R21, R22, R23 and R24 each independently denote hydrogen atom or lower alkyl group, and among these, two adjacent groups, together with carbon atoms of phenyl ring that they are bonded to, may bond to form a 5-membered ring or 6-membered ring optionally having 1 or more alkyl groups; and R25 denotes a hydrogen atom or lower alkyl group)
or salts thereof.

2. The drug which includes, as active component, a substance selected from the group comprising compound of formula (I) or formula (II) in accordance with Claim 1, and physiologically acceptable salts thereof, and hydrates and solvates thereof.

3. A drug in accordance with Claim 2 which is retinoid receptor agonist.

4. A drug in accordance with Claim 2 or 3 having action to enhance the action of retinoid.

5. A regulator in accordance with Claim 2 or 3 having action to inhibit the action of retinoid.

Rising Sun Communications Ltd. Terms and Conditions (Abbreviated)

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